

University of Alberta

Efficacy of 4% Trisodium Citrate Compared to Saline or Diluted Heparin Solution
in Patency of Central Venous Triple Lumen Catheters In Critically Ill Patients

by

Dominique Michaud



A thesis submitted to the Faculty of Graduate Studies and Research in partial
fulfillment of the requirements for the degree of Master of Nursing

Faculty of Nursing

Edmonton, Alberta

Spring 2003



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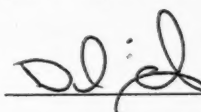
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Catheters In Critically Ill Patients**
Degree: Master of Nursing
Year This Degree Granted: 2003

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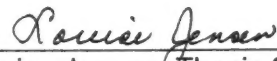
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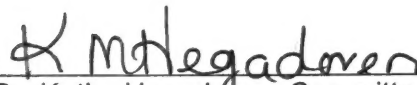
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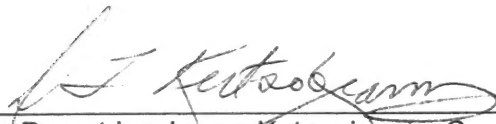
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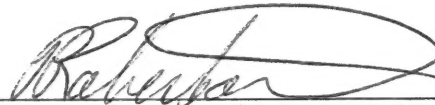
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Dedication

To my mother, Huguette, whose *joie de vivre* will always remain in my memory.

To my father, Joscelyn, for his faith and encouragement.

To my friend, Mimi, for her encouragement to pursue my education.

To my wife, Maya, for her love, patience, and support.

And most of all to my son, Marc-Olivier, who has filled my life with joy and laughter.

Abstract

The debate continues as to which solution to use in preventing catheter lumen thrombosis. The objective of this randomized, double blind study was to determine the efficacy of Trisodium Citrate solution compared to saline or diluted heparin in maintaining central venous catheter (CVC) patency in 18 critically ill patients. No statistically significant difference was found in survival time between CVCs flushed with one of these solutions ($\chi^2 = 2.45$ [2], $p = 0.2938$). Moreover, there was no increase in INR ($E [2,15; N = 105] = 1.75$, $p = 0.2081$) and PTT ($E [2,15; N = 105] = 1.67$, $p = 0.2210$), no decrease in Hgb ($E [2,15; N = 105] = 1.04$, $p = 0.3787$), platelets ($E [13,57; N = 103] = 0.36$, $p = 0.9755$), or serum ionized calcium ($E [6,20; N = 33] = 0.35$, $p = 0.9041$) in patients where CVCs were flushed with one of these solutions.

Acknowledgements

It has been my privilege to have been surrounded by scholars who created a great environment for my studies. My first thanks go to my supervisor, Dr. Louise Jensen, for her guidance and interest in my work in critical care. I am also very grateful to all of the members of my thesis committee, Dr. D. J. Kutsogiannis, Dr. P. Robertson, and Dr. K. Hegadoran, for their advice, support, and contributions to my work.

I am grateful to the people at the Royal Alexandra Hospital Intensive Care Unit, where the research took place, for their support and interest in the study. I am also grateful to the Critical Care Research team for facilitating the project. They are Pat Nicholls, Elsie Konopad, and Norine Whallen. I am thankful to Tove Larson, Sara Currie, Teddy Tanguay, and Ken Forgach for their assistance and support during this study.

This research was supported by the Royal Alexandra Hospital Foundation.

Table of Contents

	Page
CHAPTER ONE INTRODUCTION.....	1
Purpose of the Study.....	2
Significance of the Study.....	3
CHAPTER TWO LITERATURE REVIEW	5
Mechanism of Blood Coagulation.....	5
Conversion of Prothrombin to Thrombin	6
Clot Formation.....	6
Role of Calcium Ions in the Coagulation Pathway.....	7
Central Venous Catheters.....	8
Factors Affecting CVC Patency.....	9
Types of CVC Flushing Solutions.....	10
Heparin Solution.....	10
Saline Flush Solution	14
4% Trisodium Citrate Solution.....	15
CHAPTER THREE METHOD	19
Design.....	19
Sample.....	19
Definition of Terms.....	20
Data Collection Procedure	22
Central Venous Catheters.....	24
Catheter Choice	24

Catheter Insertion.....	24
Catheter Site Care	25
Selection of Ports	25
Catheter Flushing.....	26
Study Endpoint.....	28
Data Analysis	28
Ethical Considerations	29
CHAPTER FOUR FINDINGS	30
Description of the Sample	31
Comparison of Characteristics Between Groups.....	34
Demographic Characteristics per Group	34
Distribution of CVCs per Group.....	36
Anticoagulants Administered per Group.....	38
Infection Rates per Group	39
Survival Analysis of CVCs.....	39
CVC Port Total Patency Time	45
Impact of the Confounding Variables on the CVC Survival Estimates	46
Safety of 4% Trisodium Citrate Solution.....	47
INR / PTT	47
Hemoglobin and Platelets	49
Serum Ionized Calcium	52
CHAPTER FIVE DISCUSSION.....	54

Comparison of 4% Trisodium Citrate Solution, Heparin 100U/ml Solution, and Saline Solution on CVC Patency.....	56
Safety of 4% Trisodium Citrate Solution.....	59
Implications of the Study	60
Limitations of the Study.....	61
Conclusion	62
REFERENCES.....	64
APPENDIX A TRISODIUM CITRATE RESEARCH STUDY ENROLLMENT ASSESSMENT.....	76
APPENDIX B TRISODIUM CITRATE RESEARCH STUDY RESEARCH ASSISTANT GUIDE.....	78
APPENDIX C TRISODIUM CITRATE RESEARCH STUDY INFORMATION LETTER (FAMILY).....	79
APPENDIX D TRISODIUM CITRATE RESEARCH STUDY INFORMATION SHEET (PATIENT).....	82
APPENDIX E TRISODIUM CITRATE RESEARCH STUDY RANDOM ASSIGNMENT SHEET	85
APPENDIX F TRISODIUM CITRATE RESEARCH STUDY PHARMACY PROCEDURE	89
APPENDIX G TRISODIUM CITRATE RESEARCH STUDY STAFF NURSE INSTRUCTIONS	90
APPENDIX H TRISODIUM CITRATE RESEARCH STUDY SUMMARY OF THE STUDY.....	92

APPENDIX I TRISODIUM CITRATE RESEARCH STUDY BEDSIDE SHEET ...	93
APPENDIX J TRISODIUM CITRATE RESEARCH STUDY ENROLMENT LOG ON UNIT	94
APPENDIX K TRISODIUM CITRATE RESEARCH STUDY EXCLUSION LOG	95
APPENDIX L TRISODIUM CITRATE RESEARCH STUDY ADVERSE EVENTS	96
APPENDIX M TRISODIUM CITRATE RESEARCH STUDY APACHE II SCORE	97
APPENDIX N TRISODIUM CITRATE RESEARCH STUDY CASE REPORT FORM	99
APPENDIX O TRISODIUM CITRATE RESEARCH STUDY ADMISSION TAXONOMY.....	104

List of Tables

Table	Page
1. Patient Demographic, Characteristics	32
2. Admission Diagnosis of Patients	33
3. Distribution of Patients per Treatment Group and Gender	34
4. Patient Characteristics per Treatment Group	35
5. Distribution of CVCs per Group	37
6. Distribution of Anticoagulant per Group	38
7. Distribution of Infection of Catheter Tip per Group	39
8. Reason for Termination of the Study per Group	40
9. CVCs Total Patency Time in Minutes per Group	41
10. Trisodium Citrate Solution Group Survival Estimates Over Time	42
11. Saline Solution Survival Estimates Over Time	43
12. Failure Observed on the CVCs Side of Insertion per Group	45
13. Total Patency Time(Minutes) Per Port Without Differentiation Per Group	46
14. Statistical Analysis of the Confounding Variable Effect on the Group Difference	46
15. INR/PTT Levels per Group	48
16. Variation of INR Between and Within Groups	49
17. Variation of PTT Between and Within Groups	50
18. Hgb / PLT Levels per Group	51
19. Variation of Hgb Count Between and Within Groups	51

Table	Page
20. Variation of Platelets Count Between and Within Groups.....	52
21. Variation of Serum Ionized Calcium	53
22. Variation of Serum Ionized Calcium Within the Trisodium Citrate Group	53

List of Figures

Figure	Page
1. Coagulation Cascade: Intrinsic/Extrinsic Pathway for Initiating Blood Clotting	5
2. Conversion of Prothrombin to Thrombin and Polymerization of Fibrinogen to Form Fibrin Threads	7
3. Survival Probability Over Time of 4% Trisodium Citrate, Heparin 100U/ml, and Saline Solution Groups	44

CHAPTER ONE

INTRODUCTION

In the Intensive Care Unit (ICU) setting, central venous catheters (CVCs) are frequently used as a temporary vascular access for critically ill patients. CVCs provide access for either continuous or intermittent infusions. Catheter-related occlusion is the most common noninfectious complication seen with central venous access (Haire et al., 1990; Stephens, Haire, Kotulak, Schmit-Pokorny, & Kessinger, 1995; Uldall et al., 1993). Studies of the incidence of thrombosis in central venous catheters flushed with heparin have reported catheter-related thrombosis rates of 16% to 50% (Anderson et al., 1987; Blake, Huraib, Wu, & Uldall, 1990; Krog, Ekblom, Nystrom-Rosander, Rudberg, & Simonsson, 1987; Uldall et al., 1993). Due to the lack of an effective and safe method of keeping catheter lumens patent when using ports intermittently, catheter lifetime is limited due to intraluminal thrombosis. Occluded catheters must be removed and a new catheter inserted, which poses an unnecessary risk for the patient as well as increasing health care costs.

Diluted heparin and saline solutions are commonly used to flush catheter ports not in use to prevent thrombosis during intermittent utilization (Stephens et al., 1997). The debate continues as to which solution is most effective, heparin or saline, in preventing central venous catheter lumen thrombosis. The current literature has not provided an answer to this question, and problems with central venous catheter intraluminal thrombosis continue to occur. An alternative to

heparin or saline solutions for flushing central venous catheters is 4% Trisodium Citrate solution, which interferes with the normal clotting pathway (factors V and VIII activator) by chelating calcium and preventing clotting (Ward, 1997). Citrate is an important substrate of the Krebs's cycle and is rapidly metabolized, primarily by the liver, skeletal muscle, and renal cortex (VonBrecht, Flanigan, Freeman, & Lim, 1986). No study on citrate kinetics has been found, probably due to rapid metabolism of citrate. Trisodium Citrate minimizes systemic exposure, prevents exacerbation of any active bleeding problems, and also does not produce heparin-induced thrombocytopenia (HIT), a life-threatening condition associated with heparin use. Trisodium Citrate has recently been used in research and practice to prevent clotting of dialysis catheters between hemodialysis sessions. No adverse effects were noted with the use of 3 cubic centimeters (cc) of Sodium Citrate for long-term hemodialysis catheters (Buturovic et al., 1998). As well, Buturovic et al. reported that replacing heparin with Sodium Citrate resulted in a comparable patency rate for temporary hemodialysis catheters. However, there is a lack of evidence on the use of 4% Trisodium Citrate for maintaining patency in the unused lumens of CVCs in the critical care setting.

Purpose of the Study

The purpose of this pilot study was to determine the efficacy of 4% Trisodium Citrate solution compared to that of saline and diluted heparin solution in maintaining central venous triple lumen catheter patency in critically ill patients. The following hypotheses were tested:

1. CVCs flushed with 1 ml of 4% Trisodium Citrate solution will have a longer survival time than will CVCs flushed with 1ml of diluted heparin 100 U/ml or 1ml of 0.9% saline solution.

2. There will be no increase in international normalized ratio (INR) or partial thromboplastin time (PTT) in patients in whom the CVC is flushed with 4% Trisodium Citrate compared with 1ml of diluted heparin 100U/ml or 1ml of 0.9% saline solution.

3. There will be no decrease in hemoglobin (Hgb) or platelets in patients in whom the CVC is flushed with 1ml of 4% Trisodium Citrate compared with 1ml of diluted heparin 100U/ml or 1ml of 0.9% saline solution.

4. There will be no decrease in serum ionized calcium in patients in whom the CVC is flushed with 1ml of 4% Trisodium Citrate.

The effects of age, gender, site of CVC insertion, side of the catheter (left or right), length of CVC, body mass index (BMI), whether the patient was receiving anticoagulant therapy, health status (APACHE II score), infusion of antibiotics, infusion of blood product, number of IV flushes per 24-hour period, and infection of the catheter tip were also examined.

Significance of the Study

In this study, 4% Trisodium Citrate will be examined in maintaining patency for central venous triple lumen catheters was examined. The results may lead to a more consistent approach related to CVC flushing. Patients may no longer be exposed to heparin, which can induce HIT or bleeding. Also, by decreasing the thrombosis rate related to the use of heparin or saline solutions,

catheter-related sepsis may be decreased, which is a major cause of nosocomial bloodstream infections. Evidence is required to establish whether 4% Trisodium Citrate is a safe and efficacious solution to maintain CVC patency. The efficacy of 4% Trisodium Citrate as an anticoagulant has been established previously in continuous renal replacement therapy. However, more research needs to be done for the use of this solution for flushing CVCs in critically ill patients.

CHAPTER TWO

LITERATURE REVIEW

Mechanism of Blood Coagulation

Over 40 different substances affect blood coagulation, some promoting coagulation (procoagulants), others inhibiting coagulation (anticoagulants). The balance between these two groups of substances determines the coagulation status of blood. Usually, the anticoagulant group is predominant, and the blood remains anticoagulated. However, when a vessel is ruptured or the blood is in contact with an extracorporeal substance such as a catheter or filter, the activity of the coagulant factors increases, and a fibrin clot can develop. The coagulation cascade is described in Figure 1.

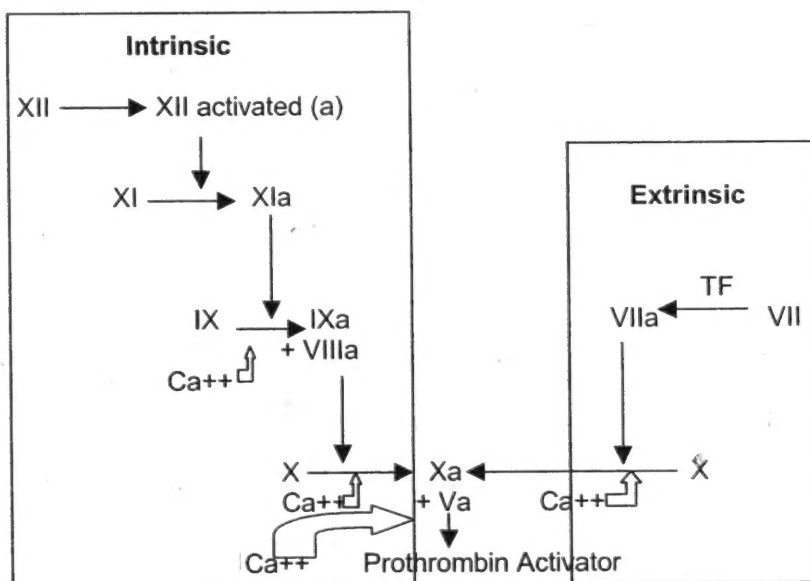


Figure 1. Coagulation cascade: intrinsic/extrinsic pathway for initiating blood clotting (Eby, 1999; Ganong, 1999; Guyton & Hall, 1996)

Conversion of Prothrombin to Thrombin

Prothrombin is a plasma protein formed continuously by the liver, with a molecular weight of 68,700 Daltons (Guyton & Hall, 1996). This protein is easily split into smaller molecules called *thrombin*. Thrombin is essential in clot formation. Prothrombin activator is an enzyme used to convert prothrombin to thrombin. The rate of formation of thrombin from prothrombin is almost directly proportional to the quantity of prothrombin activator available, which itself is approximately proportional to the degree of trauma or contact with other tissue elements outside the blood vessel endothelium (such as a catheter; Guyton & Hall, 1996). Moreover, the rapidity of the clotting process is proportional to the quantity of thrombin formed. Prothrombin activator can be formed in two ways: (a) the extrinsic pathway that begins with trauma to the vascular wall and surrounding tissues, or (b) the intrinsic pathway that begins in the blood itself (Ganong, 1999).

Clot Formation

Fibrinogen is a high molecular weight protein (340,000 Daltons) formed in the liver (Ganong, 1999) and is one of the essential factors in the coagulation pathway. Thrombin is an enzyme that acts to remove certain peptides from the fibrinogen molecules. The newly formed molecule, fibrin monomer, has the capability of polymerizing with other fibrin monomer molecules. Fibrin is initially a loose mesh of interlacing strands. It is converted by the formation of covalent cross-linkages to a dense, tight aggregate by calcium and the catalytic factor XIII activated (Ganong, 1999). At the early stage, the reticulum of the clot is weak

and can easily be broken apart. Weak noncovalent bonds between the fibrin monomers have been found to be the cause of that weakness. In order to strengthen the fibrin reticulum, another process must occur. This process involves a substance called fibrin-stabilizing factor, which is present in small amounts in plasma globulin and also released from platelets entrapped in the clot. To be activated, the fibrin-stabilizing factor requires thrombin to initiate fibrin formation. As a result, this enzyme will form covalent bonds and multiple cross-linkages between fibrin monomer molecules, adding strength to the fibrin thread clots (Figure 2).

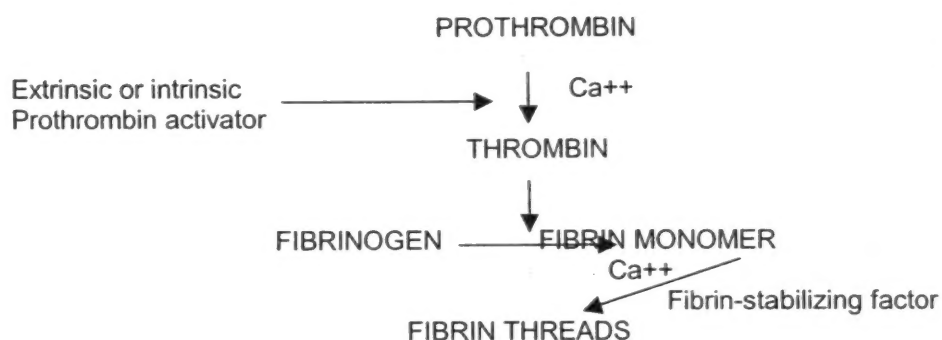


Figure 2. Conversion of prothrombin to thrombin and polymerization of fibrinogen to form fibrin threads (Ganong, 1999; Guyton & Hall, 1996).

Role of Calcium Ions in the Coagulation Pathway

Calcium ions are required for promotion of all of the reactions that occur in the coagulation cascade for both the intrinsic and extrinsic pathways. Therefore, in the absence of calcium ions, blood clotting will not occur. Fortunately, in the living body the calcium ion concentration rarely falls low enough to significantly

affect the kinetics of blood clotting. Before calcium ion concentration falls this low, the diminished level of calcium ions will likely be fatal by causing tetany throughout the body, especially of the respiratory muscles (Guyton & Hall, 1996).

Central Venous Catheters

For critically ill patients, the use of central venous catheters (CVCs) has become commonplace. CVCs are used for infusion of pharmacotherapies, resuscitative and maintenance fluids, parenteral nutrition, blood products, monitoring of hemodynamic status, and blood sampling. The use of CVCs provides a more reliable source of intravenous access than does peripheral vascular access (Baranowski, 1993).

Controversy persists as to which solution should be used to flush CVCs between intermittent utilization in order to prevent occlusion due to catheter-related thrombosis. Catheter-related thrombotic occlusion is a frequent complication of CVCs (Haire et al., 1990; Krzywda, 1998; Uldall et al., 1993; Whitman, 1996). Studies of the incidence of thrombosis in central venous catheters flushed with heparin have reported catheter-related thrombosis rates of 16% to 50% (Anderson et al., 1987; Blake et al., 1990; Krog et al., 1987; Uldall et al., 1993). Once a central venous catheter is placed in the vascular system, fibrin deposition begins on the exterior and intraluminal catheter surfaces (Buswell, & Beyea, 1998). As these deposits continue to develop, they can rapidly lead to several different types of thrombotic events, including complete intraluminal thrombus. Intraluminal thrombus accounts for up to 25% of all catheter occlusions (Andris & Krzywda, 1999). The thrombus formation that occurs when

blood contacts the foreign surface of a catheter is caused not only by activation of the extrinsic pathway, but also by direct platelet adhesion.

Occluded catheters must be removed and a new catheter inserted. This practice exposes the patient to increased risks. During CVC placement, pneumothorax, hemothorax, nerve injury, misplacement, arrhythmias, and other complications can occur (Baranowski, 1993; Randolph, Cook, Gonzales, & Pribble, 1996). Placement of a catheter in a large vessel also increases the risk of deep vein thrombosis, which can lead to pulmonary embolism (Monreal et al., 1996). Catheter-related central vein thrombosis is closely linked to catheter-related sepsis, which is a major cause of nosocomial bloodstream infections (Randolph, 1998; Timsit et al., 1998). Moreover, investigators found that the risk of catheter-related sepsis was 2.62-fold higher when catheter-related central vein thrombosis occurred (Timsit et al., 1998). For these reasons, patent CVCs are essential in order to provide access, decrease or avoid complications due to line changes, decrease catheter-related sepsis, and decrease the cost associated with catheter replacement.

Factors Affecting CVC Patency

Several factors have been identified in the literature which can influence CVC thrombosis. In rats, age has been related to changes in blood coagulation, such as increases in factors II, V, VII, VIII, IX, and XII activities (Nobukata, Ishikawa, Obata, & Shibutani, 2000). As well, Craft, May, Dorigo, Hoy, and Plant (1996) found that complications were more common with Hickman catheters in male patients and in obese patients. The same investigators also suggested that

catheters placed on the left side of the body were more likely to malfunction or block; however, no rationale was suggested to explain this finding. Furthermore, drug precipitation has been related to CVC occlusions (Harris & Maguire, 1999). The site of the catheter insertion has also been associated with different catheter failure rates. Abidi et al. (2000) found that internal jugular and subclavian catheter sites are at high risk for occlusion compared to more peripherally located catheters (femoral). It is possible that a higher number of intravenous flushes may lengthen catheter survival time; however, this has not been studied. In contrast, the length of the CVC may reduce the catheter survival time by increasing the risk of intraluminal thrombosis (more plastic exposed to blood). The relationship between catheter-related thrombogenesis and catheter-related sepsis has been closely associated (Raad et al., 1994; Timsit et al., 1998). No literature was found regarding the rate of intraluminal thrombosis with the use of a volumetric pump or a buretrol. However, the use of a buretrol may decrease the survival time by creating higher intermittent infusion compared to a volumetric pump, in which the infusion is continuous.

Types of CVC Flushing Solutions

Heparin Solution

The original designers and producers of CVCs recommended heparin flush regimens to prevent thrombosis and maintain patency (Stephens et al., 1997). Heparin is a heterogeneous mixture of highly sulfated polysaccharides of various lengths (3,000 to 50,000 Daltons; Eby, 1999). The anticoagulation activity is restricted to a unique pentasaccharide motif which binds to antithrombin III

(AT III), inducing a conformation change that increases the rate of AT III binding and inhibition of factor Xa and thrombin (Tollefsen & Blinder, 1995). Heparinized saline has enjoyed many years as the solution of choice for the maintenance of intermittent-use CVCs. Inconsistencies are evident, as shown in a survey of CVC flushing practices at 92 health care institutions. Clemence, Walker, and Farr (1995) found that 78% used 100 units (U)/ml heparin, and the remainder used 10 U/ml heparin or saline flush solutions. The results of the survey also revealed that flushing schedules varied from three times daily to twice daily to once daily.

Similar inconsistencies have been found with long-term CVCs (such as Broviac or Hickman catheters). Maintenance varied from flushing daily with 10 U/ml heparin, (Anderson et al., 1987; Anderson & Holland, 1992), every second day with 100 U/ml heparin (Krog et al., 1987), daily with 1000 U/ml heparin (Reed et al., 1983) or after each use with 5000 U/ml heparin (Blake et al., 1990; Uldall et al., 1993). Stephens et al. (1997) reported that no published studies involving short-term CVCs have demonstrated the superiority of one heparin flush regimen over another for maintaining patency. Moreover, researchers found that no studies have demonstrated a relationship between heparin flushing and reduction of catheter thrombosis (Stephens et al., 1997).

Flushing of CVCs with heparin has become a routine practice in critical care areas. The lack of evidence-based literature leads to a wide variety of flushing regimens, with no agreement on the optimal heparin concentration and frequency of heparin flushes (Delva et al., 1998; Kelly, Dumenko, McGregor, & McHutchion, 1992). Thus no clear guidelines have been developed regarding the

dose or frequency of heparin administration. The concentration of solution varies between institutions, although the most common concentration of heparin used is 100 U/ml (Baranowski, 1993; Viall, 1990). The frequency of the procedure also varies greatly. Triple lumen short-term catheters are flushed anywhere from every 8 to 12 to 24 hours depending on the hospital policy (Viall, 1990).

Stephens et al. (1997) stated, "Heparin flush solutions have become routine, and many consider the practice innocuous. Because of that attitude, patients may inadvertently receive clinically significant amounts of heparin" (p. 188). Several complications associated with unmonitored heparin flushes can occur. Unmonitored heparin flushes may lead to an overdose of heparin and iatrogenic hemorrhage, which has been termed *heparin flush syndrome* (Passannante & Macik, 1988; Rama, Haake, Bander, Ghasem-Zadeh, & Gorla, 1991). Heparin flush syndrome is a hemorrhage caused by routine unmonitored use of heparin in heparin flush solutions (arterial line and CVC) (Passannante & Macik, 1988; Rama et al., 1991; Stephens et al., 1997). Although bleeding is unlikely to occur with small doses of heparin sodium used to flush catheters (usually 10 to 100 U/ml), it can occur when the patient receives multiple flushes (Garrelts, 1992).

Autoimmune-mediated heparin-induced thrombocytopenia (HIT) is another complication which occurs in approximately 2% to 3% of all heparin-treated individuals (Fareed et al., 1999; Warkentin & Kelton, 1990). Heparin-induced thrombocytopenia (HIT) is a potentially life-threatening adverse reaction to heparin. It is mediated by multimolecular complexes consisting of platelet factor 4

(PF-4)-heparin-IgG, which binds to platelets via platelet receptors, resulting in platelet activation, platelet aggregation, and enhanced thrombin generation, with an increasing risk of developing thrombosis (Ranze, Ranze, Magnani, & Greinacher, 1999). There are two types of HIT. HIT type I is characterized by a transitory, slight, and asymptomatic reduction in platelet count (rarely below $100 \times 10^3/L$), occurring the first 1-2 days of therapy, which resolves spontaneously (Fabris et al., 2000). HIT type II, which has an immunologic origin, is characterized by a significant reduction in platelets (greater 30%) generally after the fifth day of heparin therapy and usually resolves in 5-15 days after therapy has been suspended, but in some cases may take months (Fabris et al., 2000).

This catastrophic complication of HIT type II when using heparin is associated with both full-dose and low-dose heparin flushes (Stephens et al., 1997). The majority of cases of HIT occur in medically and surgically treated adults (Warkentin & Kelton, 1990). HIT type II leads to life-threatening arterial and venous thrombosis (Heeger & Backstrom, 1986). Patients developing HIT type II suffer from complications such as myocardial infarction, stroke, venous thrombosis, pulmonary embolism, and smaller vessel occlusion characterized by complications such as diffuse mental confusion and renal failure (Fareed et al., 1999). Patients with clinically diagnosed HIT type II have a 35% probability of developing a clinically significant thrombosis (Eby, 1999; Warkentin & Kelton, 1990). Moreover, HIT type II carries a mortality of 25% to 30% and amputation rates of up to 25% (Warkentin & Kelton, 1990). The elevated incidence of mortality associated with HIT type II reflects the combined morbidity of underlying

diseases and complications generated by HIT-mediated thromboembolic events such as pulmonary embolism, stroke, myocardial infarction, and limb gangrene (Aster, 1995).

Saline Flush Solution

Numerous studies of peripheral intermittent infusion devices have demonstrated that heparin and saline are equally effective for maintaining patency (Ashton, Gibson, & Summers, 1990; Garrelts, LaRocca, Ast, Smith, & Sweet, 1989; Geritz, 1992; Golberg, Sankaran, Givelichian, & Sankaran, 1999; Kleiber, Hanrahan, Fagan, & Zittergruen, 1993; Kotter, 1996; Tuten & Gueldner, 1991). As Stephens et al. (1997) noted, some investigators have suggested that heparin flushing in CVCs is ineffective and of no greater value than flushing with saline in preventing catheter thrombosis (Ebbs, Saunders, & Baum, 1989).

In contrast, Rabe et al. (2002) found that short-term central venous triple lumen catheter sealed saline solution was not as effective in maintaining CVCs patency as were heparin (5000 IU/ml) and vitamin C (200mg/ml). Moreover, the use of 0.9% saline solution to maintain the patency of long-term (tunneled) central catheters was clearly not recommended by Buswell and Beyea (1998). In their review of the literature, Buswell and Beyea found that a low concentration of diluted heparin solution (100 IU/ml) is the most effective in maintaining patency of long-term catheters.

4% Trisodium Citrate Solution

4% Trisodium Citrate has been used for over 35 years to prevent coagulation of extracorporeal blood circuits for both dialysis and apheresis (Ward, 1997). As an anticoagulant, its use extends back to 1914 to prevent coagulation in blood products (Ashouri, 1986). 4% Trisodium Citrate combines with calcium in the blood, interfering with the normal clotting pathway (Boyd & Felton, 1986) by chelating calcium and preventing clotting (Bohler, Schollmeyer, Dressel, Dobos, & Horl, 1996; Ward, 1997). Specifically, Trisodium Citrate in the blood will chelate a portion of the ionized calcium, leading to a decrease in the ionized concentration (Mehta, McDonald, Aguilar, & Ward, 1990; Meir-Kriesche, Finkel, Gitomer, & DuBose, 1999).

Because citrate is an important substrate of the Krebs cycle (VonBrecht et al., 1986), upon entering the blood stream Trisodium Citrate is metabolized by the liver, skeletal muscle, and the proximal tubules of the kidneys (Breiterman-White, 1995), and is broken down to sodium bicarbonate (Ward, 1997). Unmetabolized Trisodium Citrate is excreted in the urine (Dzik & Kirkley, 1988). This minimizes systemic exposure and prevents exacerbation of any active bleeding problems (Reynolds, Baldwin, & Macnab, 2000) or the development of HIT. In a study comparing the utilization of citrate employed as anticoagulant in patients with acute hepatic failure and subjects with normal liver function, the elimination half life was prolonged (49.7 ± 5.4 vs 32.9 ± 1.2 min, $p < 0.05$; Apsner et al., 1997)

Of greatest concern with Trisodium Citrate flushing is the possibility of systemic hypocalcemia that can adversely cause cardiac dysrhythmias. When Trisodium Citrate is infused too rapidly, paresthesias, muscle cramps, and tetany can occur (Hocken & Hurst, 1987). The rapid systemic elimination of citrate usually prevents the development of arrhythmias during administration of citrate at rates used for anticoagulant. However, in large doses it is possible to induce such adverse affects. In one study, 1cc of 4% Trisodium Citrate (136 mmol/l) was injected every 24 hours per port (up to 3cc; 0.408 mmol/day). In comparison, when a patient is receiving a blood transfusion, he/she will receive 1.66g of Sodium Citrate Dihydrate (5.6 mmol/packed cells blood bag), 41 times greater than the proposed concentration. To achieve elevations in serum citrate at which hemodynamic evidence of hypocalcemia is demonstrated, it would be necessary to infuse multiple units of citrated blood at a very rapid rate; for example, as fast as 1 unit (500ml) every three to four minutes to a patient weighting 70 kilograms (kg) (Bunker, Bendixen, & Murphy, 1962).

One of the first groups to utilize Trisodium Citrate for regional anticoagulation during hemodialysis procedures complicated by active bleeding at the time of dialysis was Pinnick, Wiegmann, and Diedrich (1983). The results of their research using clotting time and activated partial thromboplastin times (PTTs) indicate that Trisodium Citrate infusions did not result in any cases of systemic anticoagulation. Lohr, Slusher, and Diederich (1989) compiled data collected from 326 dialysis runs in 49 hemodialysis patients at high risk for bleeding. The investigators examined the safety of Sodium Citrate and measured

serum citrate concentrations to document any systemic citrate toxicity. There was no systemic anticoagulation as measured by PTTs, and no bleeding was noted. The direct comparison of Trisodium Citrate to heparin demonstrated the safety and efficacy of Trisodium Citrate (Flanigan, VonBrecht, Freeman, & Lim, 1987). In hemodialysis, Trisodium Citrate is currently used as an anticoagulant for patients at high risk of bleeding and has been used for more than a decade.

The most commonly used form of anticoagulation for continuous renal replacement therapy in the past, low-dose heparin, caused bleeding in 10% to 50% of patients (Abramson & Niles, 1999). For this reason, citrate anticoagulation has been used as an alternative to heparin anticoagulation in continuous venovenous hemodiafiltration (CVVH). Trisodium Citrate anticoagulation has been successfully used with hemodialysis for several years (Flanigan et al., 1987; Hocken & Hurst, 1987). Regional anticoagulation with Trisodium Citrate is an effective and safe form of anticoagulation for continuous venovenous hemodiafiltration in critically ill patients with a high risk of bleeding (Kutsogiannis, Mayers, Chin, & Gibney, 2000; Palsson & Niles, 1999). Regional anticoagulation with 3.9% Trisodium Citrate is easy to use and has been shown to prolong filter life without systemic anticoagulation in continuous venovenous hemodiafiltration (Kutsogiannis et al., 2000). Moreover, in continuous arteriovenous hemodialysis (CAVHD), regional Trisodium Citrate anticoagulation has proven to minimize the risks of hemorrhage and thrombocytopenia encountered with heparin use (Mehta et al., 1990). Currently, it is the anticoagulation of choice for patients on continuous renal replacement therapy.

Also, Buturovic et al. (1998) evaluated whether replacing heparin with citrate could ensure satisfactory hemodialysis catheter patency without exposing patients to the risk of systemic heparinization. Thirty end-stage (kidney failure) patients were enrolled in the prospective study. Their findings indicate that replacing heparin with Trisodium Citrate results in a comparable patency rate for temporary hemodialysis catheters. Moreover, the same researchers reported no systemic anticoagulation or other clinically relevant side effects. Recently, Michaud, Komant, and Pfefferle (2001) published a case report where 4% Trisodium Citrate was used to maintain hemodialysis catheter patency in a critically ill patient. The patient experienced no complications or adverse effects when the hemodialysis catheter was flushed with 3ml of 4% Trisodium Citrate per port. Moreover, no hypocalcemia, bleeding, or arrhythmia occurred.

Trisodium citrate is also used for many different situations as an anticoagulant. Citrate solutions of low concentration are used to store whole blood when collected from a patient in an effort to avoid coagulation (Suontaka et al., 1996). In addition, Trisodium Citrate is used in vacuum tubes for coagulation assays (i.e., INR/PTT) in order to prevent coagulation, which could affect the laboratory results (Adcock, Kressin, & Marlar, 1997). Consequently, the use of Trisodium Citrate to maintain CVC patency seems indicated.

CHAPTER THREE

METHOD

The purpose of this study was to determine the efficacy of 4% Trisodium Citrate solution compared to 0.9% saline solution or diluted heparin 100U/ml solution in maintaining central venous triple lumen catheter (CVC) patency in critically ill patients.

Design

This pilot study was a double-blind, randomized, controlled trial. Patients were randomized to one of three treatment groups: Group A (heparin 100 IU/ml), Group B (4% Trisodium Citrate), and Group C (0.9% saline). Catheter survival time was measured from the day the patient had the central venous triple lumen catheter inserted and a port was intermittently locked, to the point at which one port of the CVC became nonpatent, the CVC was removed/changed/rewired, or the patient met one of the exclusion criteria during the study.

Sample

All general medical and surgical patients admitted to the intensive care unit (ICU) at the Royal Alexandra Hospital (Edmonton, Alberta) between November 15th, 2000, and June 15th, 2002, were evaluated for admission into the study (Appendix A). The inclusion criteria were:

1. age $\geq$ 18;
2. has a central venous triple lumen access (subclavian, jugular, or femoral) inserted for medical reasons; and

3. not receiving any medications known to affect coagulation (investigational agent, coumadin, and intravenous heparin, streptokinase, urokinase, or t-PA) for at least three days prior to the beginning of the study. Only patients with subcutaneous prophylactic heparin and low molecular weight heparin could be enrolled.

The exclusion criteria were:

1. contraindications to the use of heparin such as (a) history of heparin-induced thrombocytopenia; (b) previous untoward reaction to heparin; (c) thrombocytopenia (platelet count $< 40,000/\text{mm}^3$); (d) evidence of nonreversible coagulopathy (INR > 2.5 or PTT > 70 or fibrinogen $< 1.00\text{gm/l}$); and (e) clinical judgement of physician when active bleeding from surgical/traumatic wounds or cerebral hemorrhage happen;

2. contraindications to the use of 4% Trisodium Citrate anticoagulation such as (a) profound metabolic or respiratory alkalosis (serum pH > 7.60); and (b) serum sodium $> 160\text{ mmol/l}$; and

3. insertion of a CVC, which took place outside the ICU.

Using a block random assignment procedure (12 patients per block with equal number of patients per group), a total of 19 patients with central venous triple lumen catheters were enrolled in the study over a period of 19 months.

Definition of Terms

Patency is the ability to flush the catheter without having any resistance. A patent catheter allows the instillation of fluids but obstructs aspiration from the port.

Nonpatency is the inability to flush the catheter (resistance) and to withdraw blood after three attempts.

Catheter survival time is the time elapsing between enrollment in the study with the first flush of the study solution and the experience of nonpatency of the port, or if the CVC is rewired/removed.

Saline flush solution is an intravenous fluid (bacteriostatic sodium chloride 0.9%) without the addition of heparin. Bacteriostatic sodium chloride 0.9% has been recommended as an alternative to diluted heparin by the Canadian Intravenous Nurses Association (1999) for final flush.

Diluted heparinized solution is an intravenous fluid (bacteriostatic sodium chloride 0.9%) with the addition of anticoagulant heparin (100 USP units/ml). Heparin solution 100 U/ml will be used, because this is the most commonly cited in the literature.

4% Trisodium Citrate flush solution is an intravenous fluid (bacteriostatic sodium chloride 0.9%) with the addition of 4% Sodium Citrate. The concentration of the Trisodium Citrate was determined based on research available (Buturovic et al., 1998).

Short-term catheter is a central venous catheter used for an acute care process. The catheter is not intended to stay inserted for more than 15 days and can be inserted without surgery.

Long-term catheter is a central venous catheter used for a chronic process (i.e., long-term hemodialysis, outpatients total parenteral nutrition). The catheter is

intended to stay for several months, even years, and needs to be surgically implanted.

Catheter infection is described as isolation of >15 colony forming units on the catheter tip.

Data Collection Procedure

The site coordinator (critical care clinical nurse specialists/research coordinator) managed the data collection of the study. This included informational programs to generate interest and support for the study and the education and training of research assistants. To ensure data integrity, a random sample of 10% of the data ($N = 2$) were submitted to a chart audit.

Research assistants used a step-by-step procedure to assess what they had to do for each patient enrolled in the study (Appendix B). Each morning the Research Assistants reviewed all medical records of patients admitted to the ICU to determine eligibility for the study. Any time a patient was admitted to the ICU, the research assistant was reached by pager to determine eligibility for the study. If eligibility criteria were met, consent was then obtained (Appendixes C and D). If consent for the study prior to the CVC insertion was not obtained, the patient was not eligible for the study. The patient was randomized to either 4% Trisodium Citrate, saline, or diluted heparin solution by the Pharmacy Department following the pre-generated block random assignment sheet (Appendix E). Unmarked vials with specific solution and reference codes were prepared and distributed to the ICU by the Pharmacy Department.

The Pharmacy Department at the Royal Alexandra Hospital had a procedure guideline to follow for randomization (Appendix F). The pharmacist had the reference code, which remained unknown until the completion of the study. When necessary, it was possible to break the reference code if thrombocytopenia (HIT positive) was diagnosed, if the physician was concerned that heparin was the cause of active bleeding for the patient, or if the patient met one of the exclusion criteria during the study. If HIT was suspected, HIT assay was drawn only once when the platelet count fell below 30% of the baseline in order to determine whether the patient was HIT positive. If a HIT positive result was diagnosed, the patient was removed from the study and the reason for the exclusion recorded in the Case Report Form. The research assistant and staff nurse were unaware of the solution assignment. When a study solution was assigned to the patient, the research assistant gave instructions to the nursing staff about his/her role in the study (Appendix G). The nursing instructions and a summary of the study (Appendix H) were kept in the front of the patient's chart. It was the responsibility of the research assistant to post the bedside sheet (Appendix I) in each room to indicate that the patient was in the study. Moreover, instructions were given to the physicians regarding the catheter insertion and initial flushing. The research assistant was responsible for collecting the patient data on a daily basis. Moreover, each patient enrolled was entered on an Enrolment Log (Appendix J) that was kept in the research assistant's office. Each patient excluded was also recorded on an Exclusion Log (Appendix K). Any adverse events such as bleeding, drop in platelets (more 30% from baseline),

arrhythmia (ventricular fibrillation, ventricular tachycardia, frequent premature ventricular complexes [PVC], and torsade de pointe), hypocalcemia (ionized calcium below 0.85 mmol/l), if it became HIT positive, and QT prolongation were recorded on the Adverse Events Form (Appendix L).

Factors other than diluted heparin, saline, or 4% Trisodium Citrate may affect the survival time and patency of the CVC. For this reason, age, gender, site of CVC insertion, side of the catheter (left or right), length of CVC, body mass index (BMI), whether the patient was receiving anticoagulants therapy, health status (APACHE II score), infusion of antibiotics, infusion of blood products, number of IV flushes per 24-hour period, and infection of the catheter tip were recorded (Appendix N).

Central Venous Catheters

Catheter Choice

Only central venous triple lumen catheters were used for the study. In order to reduce the variability that may occur between different catheters, Baxter catheters (stock # M316 F or #M320 F) were used for this study. These catheters were not coated with any anticoagulant, antiseptics, or antibiotics.

Catheter Insertion

Under strict aseptic conditions, central venous triple lumen catheters were inserted at the bedside using the Seldinger technique. Physicians were required to wear a mask, sterile gloves, and gown. The insertion site was prepared with Betadine and draped with sterile towels. Betadine was chosen instead of Chlorhexidine in order to see adequately where the patient had been prepped

prior to the insertion of the catheter. Catheters were inserted percutaneously and then covered with a dressing following the procedure as outlined below. Chest radiographs were obtained after catheter placement to ensure proper catheter position (except for femoral lines). Each port was then flushed with 10 cc of saline flush solution (Canadian Intravenous Nurses Association, 1999) prior to administration of the randomized study solution.

Catheter Site Care

0.5% chlorhexidine gluconate and 70% isopropyl alcohol impregnated swabstick or solution was used to clean the CVC site. Chlorhexidine was found to be significantly more effective in decreasing both local infection and catheter-related sepsis in CVC (Andris & Krzywda, 1997). A sterile 4x4 gauze folded in half was used to cover the catheter exit site and mifix tape attached. The four sides of the gauze were covered. A transparent dressing was not found to be superior to standard gauze in reducing the risk of infection at the site of the catheter (Maki, Stolz, Wheeler, & Mermel, 1994). The dressing was changed every day or when it became damp, loosened, or soiled, using the above procedure.

Selection of Ports

Any ports not used for continuous infusion after insertion of the central venous catheter were available for use in the study. These ports set aside for intermittent use had been flushed with the study solution and their patency assessed. If all of the ports were used after the CVC insertion, the research assistants waited until one port became intermittently used. The initial port flush

consisted of 10 cc of saline flush solution, followed by the administration of the randomized study solution.

Catheter Flushing

The same amount of study solution was injected into each port. This minimized the degree of predictability of treatment assignment. According to the Intravenous Nurses Society (1995) in the United States, each lumen of the central venous catheter has to be flushed using a positive pressure technique with a volume equal to twice its internal volume. Immediately after one of the CVC ports became available for intermittent use, the study solution was then injected. For this reason, the lumen of the CVC was flushed with 1 cc of study solution. Prior to the administration of the study solution, 10 cc of normal saline solution was injected. The study solution was drawn and injected using a 10-cc syringe to prevent excessive pressures, which could lead to catheter rupture (Canadian Intravenous Nurses Association, 1999). In order to maintain a positive pressure while flushing, the nurse had to withdraw the needle from the injection port while continuing to inject the flushing solution so that the needle was removed just as the last portion of the solution was injected into the lumen. This technique prevent a reflux of blood into the lumen (Baranowski, 1993). As noted by the American Intravenous Nurses Society, if any resistance was encountered while attempting to flush a catheter, the nurse ceased to flush and withdrew blood to a maximum of three attempts. The port was then considered nonpatent, and the subject was removed from the study. If the physician decided against changing the catheter, the port was then flushed with the solution normally used

at the Royal Alexandra Hospital Intensive Care Unit. The patient was not randomized again into the study.

The randomized study solution was injected into intermittently used catheter ports every 24 hours or after each use. Because there is no clear direction and consensus in the literature on the frequency of flushing, every 24 hours was chosen. Moreover, by reducing the frequency of flushing, the risk of infection that can be created by multiple flushes can be reduced.

If any medications are given intermittently or blood samples drawn from the port, the port must be flushed with 10 cc of saline solution after completion of the medication or blood sampling and prior to the administration of the randomized study solution (Canadian Intravenous Nurses Association, 1999). No study was found evaluating the use of Trisodium Citrate on the validity of laboratory results. However, a randomized clinical trial that compared the effects of heparin or Trisodium Citrate used to anticoagulate indwelling arterial catheters on acid-base and electrolyte measurement found that sodium citrate used to maintain arterial catheters can affect laboratory results (Cardinal, Allan, Hindmarsh, Jones, & Delisle, 2000). For this reason blood samples were not drawn from the port due to a lack of information regarding citrate. In addition, if laboratory blood work was needed for the study and was not ordered by a physician, the Trisodium Citrate Research Study had to pay for the laboratory work.

After flushing, any unused ports were clamped using the clamps provided with the CVC. Hemostats or sharp-edged clamps were not used. No stopcock or

extension tubing was attached at the end of a catheter port to limit factors that could interfere with the flushing process. Moreover, no reflux valve cap was added to any ports. Only conventional needles were used for the study, and needleless system needles were prohibited.

Study Endpoint

Central venous triple lumen catheter patency was assessed by the ability to flush the port without resistance. This is derived from the intravenous therapy guidelines (Canadian Intravenous Nurses Association, 1999). The catheter survival time was measured from the day the patient had the central venous catheter inserted and a port was intermittently locked to the point at which one port of the CVC became nonpatent, the CVC removed/changed/rewired, or the patient met the exclusion criteria or withdrew from the study. Survival time was measured in minutes. When the study was completed with the patient, the port was flushed with 10 ml of saline followed with the institution's standard flushing solution. When the CVC was removed/changed/rewired (end of the study), the catheter tip was sent for culture and sensitivity, and the microbiology report was recorded on the care report form by the research assistant. If the patient was excluded or withdrew from the study, the catheter tip was not sent for culture and sensitivity.

Data Analysis

Data were analyzed using SAS software Version 8.02. Descriptive statistics were completed for each variable. Kaplan-Meier plots were used to estimate the probability of catheter survival time and a Wilcoxon test to determine

the difference in survival time between groups. To determine the effects of identified factors that may influence catheter survival time, a one-way analysis of variance (ANOVA) or a Fisher's exact test were conducted where appropriate. A repeated measure ANOVA was used to establish whether there were differences between groups on the variables of INR, PTT, Hgb, platelets, and serum ionized calcium. The significance level was set at 0.05.

Ethical Considerations

Ethical approval was obtained from the Health Research Ethics Board (Panel A), Capital Health Region. Support from the medical officer and the patient care manager of each ICU were also obtained for the study.

Several strategies were utilized to protect the rights of the patients who agreed to participate in the study. First, following an introduction and explanation of the study, consent was obtained from an immediate family member or the patient's assigned agent (Appendix C) or the patient (Appendix D). The person was informed of the purpose of the study, that their participation was voluntary, and that they could withdraw at any time with no consequences to the nursing care.

Confidentiality of the participant was maintained, and no names were attached to data-collection forms. A coded numbering system ensured confidentiality. Their names, code numbers, and data were on separate sheets, which will be kept in separate locked file cabinets for a minimum of five years.

CHAPTER FOUR

FINDINGS

The purpose of this pilot study was to determine the efficacy of 4% Trisodium Citrate solution compared to that of 0.9% saline and diluted heparin 100 U/ml solutions in maintaining central venous triple lumen catheter patency in critically ill patients. The following hypotheses were tested:

1. CVCs flushed with 1 ml of 4% Trisodium Citrate solution will have a longer survival time than CVCs flushed with 1ml of diluted heparin 100 U/ml or 1ml of 0.9% saline solution.
2. There will be no increase in INR or PTT in patients in whom the CVC is flushed with 4% Trisodium Citrate compared with 1ml of diluted heparin 100U/ml or 1ml of 0.9% saline solution.
3. There will be no decrease in hemoglobin (Hgb) or platelets in patients in whom the CVC is flushed with 1ml of 4% Trisodium Citrate compared with 1ml of diluted heparin 100U/ml or 1ml of 0.9% saline solution.
4. There will be no decrease in serum ionized calcium in patients in whom the CVC is flushed with 1ml of 4% Trisodium Citrate.

The effects of age, gender, site of CVC insertion, side of the catheter (left or right), length of CVC, body mass index (BMI), whether the patient was receiving anticoagulant therapy, health status (APACHE II score), infusion of antibiotics, infusion of blood product, number of IV flushes per 24-hour period, infection of the catheter tip were examined as potential confounding variables.

Kaplan-Meier plots were used to estimate the probability of catheter survival time and a Wilcoxon test to determine the difference in survival time between groups. To determine the effects of identified factors that may influence catheter survival time, a one-way ANOVA or a Fisher's exact test was conducted where appropriate. A repeated measures ANOVA was used to establish whether there were differences between groups on the variables of INR, PTT, Hgb, platelets, and serum ionized calcium.

Description of the Sample

A total of 91 patients were eligible for the study, and 19 patients were enrolled in the study. The main reasons for exclusion were no family present at the time of CVC insertion for consent (39.6%), emergency CVC insertion (17.6%), receiving anticoagulant therapy less than three days prior to enrolment (12%), and CVC missed by research assistants (9.8%). One patient assigned to the 4% Trisodium Citrate group was further excluded during the study because of a drop in platelets that was more than 30% of the baseline. The final sample consisted of 18 patients aged between 42 and 88 years ($M = 58.28$, $SE = 3.19$). Seven males (38.9%) and 11 females (61.1%) were enrolled in the study. The APACHE II score ranged from 10 to 33 ($M = 19.28$, $SE = 1.60$). The patients' mean BMI was 32.90 ± 2.48 . The weight ranged from 48 to 129 kg ($M = 75.33$, $SE = 4.17$); the height ranged from 147.5 to 186 cm ($M = 166.75$, $SE = 2.34$ cm). The distribution of age, gender, APACHE II score (24 hours prior to enrollment), BMI, weight, and height are listed in Table 1.

Table 1

Patient Demographic Characteristics

Parameters	<u>M</u>	<u>SE</u>	Range
Age (y)	58.28	3.19	42-88
Male (n=7)	--	--	43-88
Female (n=11)	--	--	42-83
APACHE II	19.28	1.60	10-33
BMI	32.90	2.48	17.6-52.2
Weight (kg)	75.33	4.17	48-129
Height (cm)	166.75	2.34	147.5-186

A total of 83.3% of the patients (N = 15) had a nonoperative diagnosis and 16.7% (N = 3) had an operative diagnosis at the time of enrolment in the study. Of the nonoperative patients, four patients (22.2%) had respiratory diseases, three patients (16.67%) had gastrointestinal diseases, one patient (5.56%) had a neurological disease, two patients (11.11%) had sepsis, four patients (22.2%) experienced trauma, and one patient (5.56%) had a metabolic disorder. For the operative diagnosis, two patients (11.12%) had gastrointestinal complications and one patient (5.56%) had a trauma requiring surgery (Table 2).

Table 2

Admission Diagnosis of Patients

Admission diagnosis	Frequency	Percentage
Nonoperative		
Parasitic pneumonia	1	5.56
Bacterial/viral pneumonia	1	5.56
Asthma	1	5.56
Other respiratory disease	1	5.56
GI inflammatory disease	2	11.11
Diverticulitis	1	5.56
Subarachnoid hemorrhage	1	5.56
Sepsis (other urinary tract)	2	11.11
Head trauma	3	16.67
Multiple trauma	1	5.56
Other metabolic disorder	1	5.56
Subtotal	15	83.3
Postoperative		
GI perforation	1	5.56
GI obstruction	1	5.56
Multiple trauma	1	5.56
Subtotal	3	16.7

Comparison of Characteristics Between Groups

Demographic Characteristics per Group

Patient randomization to treatment groups was as follows: seven patients (38.9%) in the Trisodium Citrate solution group, seven patients (38.9%) in the saline solution group, and four patients (22.2%) in the heparin solution group. An analysis of the variable gender revealed no statistically significant difference between the groups ($\chi^2 = 2.97$ [8, $N = 18$], $p = 0.3287$) (Table 3). The mean age for the heparin solution group was 68.5 years (y.o.), with a standard error of 7.1 years, compared to the Trisodium Citrate solution group (54.14 ± 3.95 y.o.) and saline solution group (56.67 ± 5.54 y.o.). A one-way analysis of variance (ANOVA) revealed no statistically significant difference among the three groups ($F [2,15; N = 17] = 1.642$, $p = 0.227$) (Table 4).

Table 3

Distribution of Patients per Treatment Group and Gender

Gender	Group			p
	Heparin	Citrate	Saline	
Male	2	4	1	0.3287
Female	2	3	6	

Table 4

Patient Characteristics per Treatment Group

Group	<u>M</u>	<u>Age</u> <u>SE</u>	<u>p</u>
Heparin	68.5	7.1	0.227
Citrate	54.14	3.95	
Saline	56.57	5.54	
Group	<u>M</u>	<u>APACHE II</u> <u>SE</u>	<u>p</u>
Heparin	19	3.70	0.733
Citrate	20.86	3.33	
Saline	17.86	1.72	
Group	<u>M</u>	<u>BMI</u> <u>SE</u>	<u>p</u>
Heparin	33.95	7.63	0.687
Citrate	30.07	2.56	
Saline	35.03	4.41	
Group	<u>M</u>	<u>Weight</u> <u>SE</u>	<u>p</u>
Heparin	69.5	7.42	0.557
Citrate	81.0	9.69	
Saline	73.0	2.76	
Group	<u>M</u>	<u>Height</u> <u>SE</u>	<u>p</u>
Heparin	167.75	2.63	0.630
Citrate	169.07	5.46	
Saline	163.86	2.38	

APACHE II scores showed that the Trisodium Citrate solution group had the sickest patients (20.86 ± 3.33) compared to the heparin solution group (19 ± 3.70) and the saline solution group (17.86 ± 1.72). An ANOVA of APACHE II scores showed no statistically significant difference between the groups ($F [2,15; N = 17] = 0.317, p = 0.733$). The Trisodium Citrate solution group patients were heavier (69.5 ± 7.42 kg) and taller (169.07 ± 5.46 cm) than were the heparin and saline solution groups patients, yet weight ($F [2,15; N = 17] = 0.608, p = 0.557$) and height ($F [2,15; N = 17] = 0.477, p = 0.630$) were not statistically different between the groups. However, looking at body mass index (BMI), the saline solution group had a higher ratio (35.03 ± 4.41) than did the heparin solution group (33.95 ± 7.63) and the Trisodium Citrate solution group (30.07 ± 2.56). However, BMI showed no statistical difference between the groups ($F [2,15; N = 17] = 0.385, p = 0.687$) (Table 4).

Distribution of CVCs per Group

The majority of the patients ($N = 12, 66.7\%$) had a CVC inserted in the subclavian vein. The femoral vein ($N = 2, 22.2\%$) and the internal jugular ($N = 4, 11.1\%$) were also used as sites for catheter insertion (Table 5). The CVC site of insertion showed no statistically significant difference between the groups ($\chi^2 = 4.1250 [4, N = 18], p = 0.5296$). Seven CVCs were inserted in the left side (38.9%) of the body and 61.1% in the right side ($N = 11$) of the body. Analysis of CVC side of insertion showed a statistically significant difference between the groups

($\chi^2 = 7.6308$ [2, $N = 18$], $p = 0.0238$), with all CVCs of the Trisodium Citrate group inserted on the right side of the body (Table 5).

Table 5

Distribution of CVCs per Group

Site CVC	Group			p
	Heparin	Citrate	Saline	
IJ	0	1	3	0.5296
Femoral	1	1	0	
Subclavian	3	5	4	

Side CVC	Group			p
	Heparin	Citrate	Saline	
Left	3	0	4	0.0238
Right	1	7	3	

Length CVC	Group			p
	Heparin	Citrate	Saline	
16 cm	3	6	7	0.6797
20 cm	1	1	0	

As per ICU policy at the Royal Alexandra Hospital, the two patients (11.1%) with a CVC inserted in the femoral vein had a 20-cm-length catheter compared to the other sites of insertion ($N = 16$, 88.9%), where a 16-cm-length CVC was used (Table 5). Femoral cannulation with 20-cm-length CVC is restricted to difficult cannulation or emergency situations. CVC length showed no statistical difference between the groups ($\chi^2 = 1.7277$ [2, $N = 18$], $p = 0.6797$).

Anticoagulants Administered per Group

Anticoagulants had been administered to three patients (16.7%); 2 patients (11.1%) received a heparin infusion and 1 patient (5.6%) received Trisodium Citrate in hemodialysis. Trisodium Citrate administration has a regional filter anticoagulation and should not interfere with systemic coagulation. No statistically significant difference between the groups was found on anticoagulants administered ($\chi^2 = 3.4928$ [4, $N = 18$], $p = 0.3995$). Table 6 presents the distribution of anticoagulation used during the study by group.

Table 6

Distribution of Anticoagulant per Group

Anticoagulant	Group			p
	Heparin	Citrate	Saline	
None	3	5	7	0.3995
Heparin infusion	1	1	0	
Trisodium citrate	0	1	0	

Infection Rates per Group

Catheter tips were sent to assess nosocomial infections that could interfere with CVC patency. Only two catheter tips (11.8%) came back positive for staphylococcus coagulase negative and coryniforms bacteria. However, 47% ($N = 8$) of the CVC tips were missing, and one tip was not sent (Table 7). No statistically significant difference between the catheter tip infection rates and the groups was found ($\chi^2 = 3.5525$ [4, $N = 17$], $p = 0.4841$).

Table 7

Distribution of Infection of Catheter Tip per Group

Presence of infection	Group			p
	Heparin	Citrate	Saline	
No	3	3	1	0.4841
Yes	0	1	1	

Survival Analysis of CVCs

Looking at the reasons for termination of the study, the study was stopped in four cases (22.2%) because of nonpatency (port plugged). Nonpatency was one of the variables analyzed to establish survival time of the CVC and was considered as the uncensored observation. In most of the cases ($N = 7$, 38.9%), the study ended because the CVC was removed due to physician prescription.

Other reasons for CVC removal (CVC rewired, removed, pulled out accidentally, or patient deceased) were considered as censored observations for the remaining 14 patients (77.8%). No statistically significant difference on the reason for termination of the study was found between the groups ($\chi^2 = 7.1327$ [8, $N = 18$], $p = 0.5224$). Table 8 presents the reason for termination of the study by group.

Table 8

Reason for Termination of the Study per Group

Reason	Group			p
	Heparin	Citrate	Saline	
Uncensored Nonpatency	0	1	3	0.5224
Censored Rewired	1	1	0	
Line removed by Rx	2	3	2	
Line pulled out accidentally	0	2	1	
Deceased	1	0	1	

The first hypothesis tested was that CVCs flushed with 1ml of 4% Trisodium Citrate solution will have a longer survival time than CVCs flushed with 1ml of diluted heparin 100U/ml or 1ml of 0.9% saline solution.

The heparin solution group had the longest total patency time ($\underline{M} = 9655.0$, $\underline{SE} = 4006.12$, $\underline{Mdn} = 6237.50$) compared to the saline solution group ($\underline{M} = 7206.14$, $\underline{SE} = 1064.08$, $\underline{Mdn} = 8300.00$) and Trisodium Citrate solution group ($\underline{M} = 5200.0$, $\underline{SE} = 525.41$, $\underline{Mdn} = 5625.00$). No statistically significant difference on mean total patency time was found between the groups ($F [2, 15; N = 17] = 1.524$, $p = 0.250$) Total CVCs patency time in minutes per group are found in Table 9.

Table 9

CVCs Total Patency Time in Minutes per Group

Group	<u>N</u>	<u>M</u>	<u>SD</u>	<u>SE</u>	<u>Mdn</u>	Range	<u>p</u>
Citrate	7	5200.00	1390.11	525.41	5625.00	3310-7200	0.250
Heparin	4	9655.00	8012.24	4006.12	6237.50	4585-21560	
Saline	7	7206.14	2815.29	1064.08	8300.00	2625-10315	

The Trisodium Citrate group showed a mean and a median survival time using a Kaplan-Meier estimation of 5760 minutes (4 days). The only catheter failure that occurred in the Trisodium Citrate group occurred at day four. Table 10 shows the 4% Trisodium Citrate group survival estimates over time.

Table 10

Trisodium Citrate Solution Group Survival Estimates Over Time

Patency in minutes	Number survival	Number failure	Error	Failed	Left
0.0	1.0	0	0	0	7
3310 *	--	--	--	0	6
4020 *	--	--	--	0	5
4210 *	--	--	--	0	4
5625 *	--	--	--	0	3
5760	0.6667	0.3333	0.2722	1	2
6275 *	--	--	--	1	1
7200 *	--	--	--	1	0

* The marked survival times are censored observations.

The survival time of the heparin group was not calculated using a Kaplan-Meier estimation because no failures occurred. As mentioned previously, mean total patency in minutes for the heparin solution was 9655 minutes (6.7 days), with a standard error of 4006.12 minutes (Mdn = 6237.50). However, the heparin group total patency time mean may have been underestimated because the largest observation of the actual time until a port became nonpatent was not observed.

The saline group showed a mean survival time using a Kaplan-Meier estimation of 9317.5 minutes (6.5 days), with a standard error of 610.9 minutes. The median survival time of the saline group was 9327.50 minutes. Three

catheters became occluded at a median time of 5.8 days (5.76–7.16 days).

Table 11 illustrates the saline solution survival estimate over time.

Table 11

Saline Solution Survival Estimates Over Time

Patency in minutes	Number survival	Number failure	Error	Failed	Left
0.0	1.0	0	0	0	7
2625 *	--	--	--	0	6
5273 *	--	--	--	0	5
5560 *	--	--	--	0	4
8300	0.75	0.25	0.2165	1	3
8340	0.50	0.50	0.2500	2	2
10030 *	--	--	--	2	1
10315	0	1.0	0	3	0

* The marked survival times are censored observations

When the three solutions groups were compared, a Wilcoxon test showed no statistically significant difference in survival time ($\chi^2 = 2.45$ [2], $p = 0.2938$).

The survival probability is shown in Figure 3.

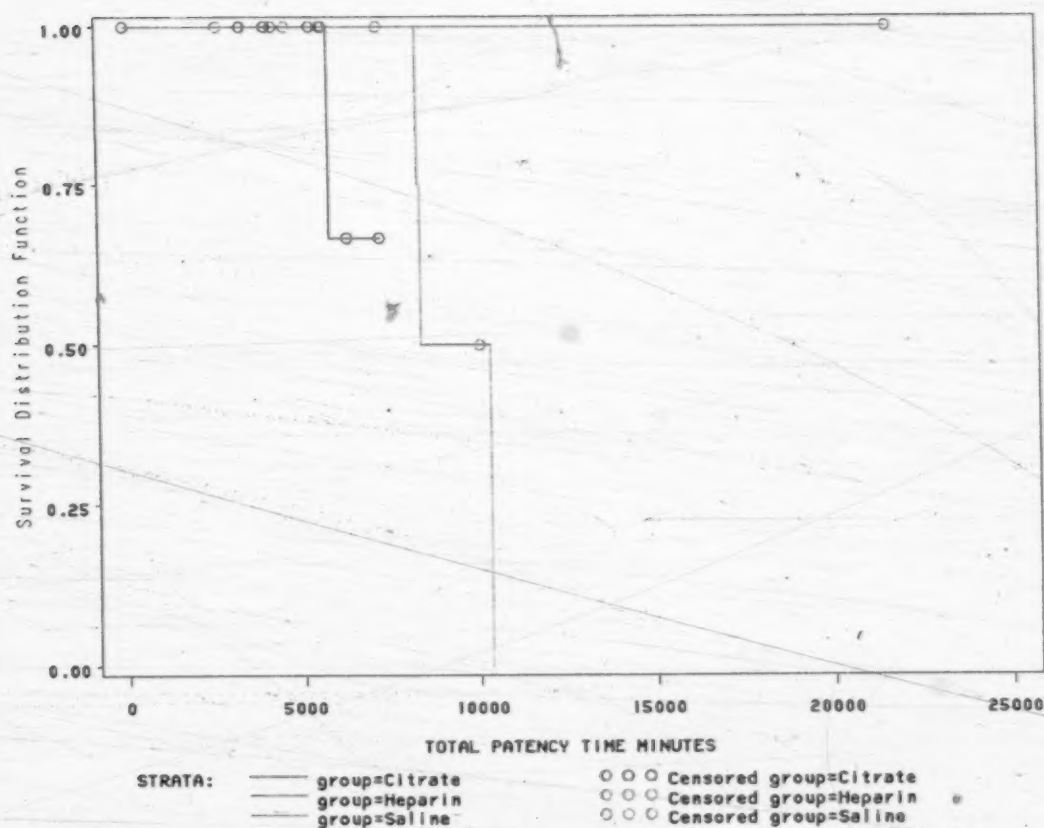


Figure 3. Survival probability over time of 4% Trisodium Citrate, heparin 100U/ml, and saline solution groups

When the impact of the variable CVCs "left" side of insertion on the survival time of the groups was considered, a Wilcoxon test could not be performed because failures on the left side of the CVC were observed in only the saline group (Table 12). When we looked at the impact of the variable CVCs "right" side of insertion on the survival time, a Wilcoxon test showed no statistically significant difference on the survival time ($\chi^2 = 1.20$ [2], $p = 0.55$).

Table 12

Failure Observed on the CVCs Side of Insertion
per Group

Group	Left side	Right side	Total
Heparin	0	0	0
Citrate	0	1	1
Saline	2	1	3
Total	2	2	4

CVC Port Total Patency Time

Total patency time of each CVC port was also calculated. The medial port was the one to be locked most often ($\bar{M} = 3328.94$, $\underline{SE} = 1084.70$), followed by the distal port ($\bar{M} = 2247.11$, $\underline{SE} = 732.58$) and the proximal port ($\bar{M} = 1930.61$, $\underline{SE} = 636.41$). Because of the small sample size ($N = 18$), and the small number of catheter failures, no survival estimates for each port per group were calculated. Table 13 presents the total patency time (minutes) of each port per group.

Table 13

Total Patency Time(Minutes) Per Port Without Differentiation Per Group

Port	<u>N</u>	<u>M</u>	<u>SD</u>	<u>SE</u>	Range
Proximal	18	1930.61	2700.04	636.41	0-9405
Medial	18	3328.94	4602.00	1084.70	35-20470
Distal	18	2247.11	3108.06	732.58	0-12115

Impact of the Confounding Variables on the CVC Survival Estimates

One-way ANOVA was performed to assess the relationship between groups and the scale variables of age, BMI, APACHE II score, and number of flushes. No statistically significant differences between the groups were found (Table 14).

Table 14

Statistical Analysis of the Confounding Variable Effect on the Group Difference

Variable	Group			F	df	p
	Saline	Heparin	Citrate			
	<u>M ± SE</u>	<u>M ± SE</u>	<u>M ± SE</u>			
Age	56.57 ± 4.93	68.50 ± 6.52	54.14 ± 4.92	1.64	2,15	0.2266
BMI	35.03 ± 4.13	33.95 ± 5.47	30.07 ± 4.13	0.39	2,15	0.6868
APACHE II	17.86 ± 2.68	19.00 ± 3.54	20.86 ± 2.68	0.32	2,15	0.7328
Number flushes	10.86 ± 4.70	22.85 ± 6.22	10.43 ± 4.70	1.36	2,15	0.2872

A Fisher's exact test was performed to assess the relationship between groups and the categorical variables of gender, CVCs sites of insertion, CVCs sides of insertion, CVCs length, anticoagulant, administration of blood product, administration of antibiotics, and CVCs tips infection. No group differences were found with gender ($p = 0.3287$), CVCs sites of insertion ($p = 0.5296$), length of the CVCs ($p = 0.6797$), anticoagulation ($p = 0.3995$), administrations of blood products ($p = 0.3137$), administration of antibiotics ($p = 0.8320$), or infection of the catheter tips ($p = 0.4841$). The CVCs side of insertion was found to be significantly different among groups ($p = 0.0238$). All CVCs of the Trisodium Citrate solution group were inserted in the right side of the body, compared to the heparin and saline solution groups, where CVCs were equally distributed between the left and right side.

Safety of 4% Trisodium Citrate Solution

INR / PTT

The second hypothesis tested was that there will be no increase in INR or PTT in patients when the CVC is flushed with 4% Trisodium Citrate compared with diluted heparin or a saline solution. A repeated measures ANOVA was used to analyze the variables INR and PTT. A total of 105 blood samples were analyzed for INR. The saline solution group had the lowest INR baseline levels ($\bar{M} = 1.11$, $SE = 0.01$), compared to the Trisodium Citrate solution group ($\bar{M} = 1.24$, $SE = 0.05$) and heparin solution group ($\bar{M} = 1.28$, $SE = 0.09$). Moreover, the saline solution group had also the lowest mean INR levels ($\bar{M} = 1.09$, $SE = 0.06$), compared to the Trisodium Citrate solution group ($\bar{M} = 1.28$,

$SE = 0.11$) and heparin solution group ($M = 1.26$, $SE = 0.08$). Table 15 presents the INR/PTT levels per group. There was no statistically significant difference between groups on mean INR levels ($F [2,15; N = 105] = 1.75$, $p = 0.2081$). Moreover, there was no statistically significant difference in mean INR levels over time ($F [15,59; N = 105] = 0.38$, $p = 0.9794$). Table 16 presents the variation of INR within and between groups.

Table 15

INR/PTT Levels per Group

<u>INR baseline</u>			
Group	M	SE	Range
Heparin	1.28	0.09	1.1-1.5
Citrate	1.24	0.05	1.1-1.4
Saline	1.11	0.01	1.1-1.2

<u>Mean INR levels</u>			
Group	M	SE	Range
Heparin	1.26	0.08	1.1-1.5
Citrate	1.28	0.11	0.9-1.6
Saline	1.09	0.06	1.1-1.4

<u>PTT baseline</u>			
Group	M	SE	Range
Heparin	39.00	5.85	23-51
Citrate	30.86	2.69	22-42
Saline	25.43	1.19	21-30

<u>Mean PTT levels</u>			
Group	M	SE	Range
Heparin	38.19	4.51	23-52
Citrate	33.35	4.00	21-54
Saline	28.95	2.34	23-56

Table 16

Variation of INR Between and Within Groups

Parameters	F	df	p
Between groups			
• Group	1.75	2	0.2081
• Patient (group) (between subject error)	--	15	
Within groups			
• Time	0.38	15	0.9794
• Group*time	0.51	13	0.9094
• Within subject error	--	59	

The 105 blood samples were also analyzed for PTT levels. The saline solution group had the lowest PTT baseline level ($\bar{M} = 25.43$, $\underline{SE} = 1.19$) and mean PTT levels ($\bar{M} = 28.95$, $\underline{SE} = 2.34$), compared to the Trisodium Citrate and heparin solution groups (Table 15). There was no statistically significant difference between groups on mean PTT levels ($F [2,15; N = 105] = 1.67$, $p = 0.2210$). Moreover, there was no statistically significant change over time in mean PTT levels ($F [15,59; N = 105] = 1.66$, $p = 0.0848$). Table 17 presents the variation of PTT within and between groups.

Hemoglobin and Platelets

The third hypothesis tested was that there will be no decrease in hemoglobin (Hgb) or platelets (Plt) in patients when the CVC is flushed with 4% Trisodium Citrate compared with diluted heparin 100U/ml or a saline solution. A repeated measures ANOVA was used to analyze the hemoglobin and platelets levels. A total of 105 blood samples were analyzed for the Hgb. The heparin

Table 17

Variation of PTT Between and Within Groups

Parameters	F	df	P
Between groups			
• Group	1.67	2	0.2210
• Patient (group) (between subject error)	--	15	
Within groups			
• Time	1.66	15	0.0848
• Group*time	0.47	13	0.9314
• Within subject error	--	59	

solution group had the highest Hgb baseline levels ($\underline{M} = 103.50$, $\underline{SE} = 12.82$), compared to the Trisodium Citrate solution group ($\underline{M} = 91.29$, $\underline{SE} = 4.00$) and the saline solution group ($\underline{M} = 98.43$, $\underline{SE} = 6.40$). Moreover, the heparin solution group had the highest mean Hgb levels ($\underline{M} = 98.38$, $\underline{SE} = 7.63$), compared to the Trisodium Citrate solution group ($\underline{M} = 94.30$, $\underline{SE} = 4.81$) and the saline solution group ($\underline{M} = 89.64$, $\underline{SE} = 2.53$). Table 18 presents the Hgb/Plt levels per group. There was no statistically significant difference between groups on mean Hgb levels ($\underline{F} [2,15; \underline{N} = 105] = 1.04$, $p = 0.3787$). Moreover, the mean Hgb levels did not significantly change over time ($\underline{F} [15,59; \underline{N} = 105] = 1.42$, $p = 0.1690$). Table 19 presents the variation of Hgb levels within and between group.

Table 18

HgB / PLT Levels per Group

<u>Hgb baseline</u>			
Group	M	SE	Range
Heparin	103.50	12.82	82-136
Citrate	91.29	4.00	72-104
Saline	98.43	6.40	82-132
<u>Mean HgB levels</u>			
Group	M	SE	Range
Heparin	98.38	7.63	76-125
Citrate	94.30	4.81	75-120
Saline	89.64	2.53	65-110
<u>PLT baseline</u>			
Group	M	SE	Range
Heparin	174.25	33.89	114-269
Citrate	195.29	56.56	43-282
Saline	272.71	67.96	102-607
<u>Mean PLT levels</u>			
Group	M	SE	Range
Heparin	210.92	16.73	137-321
Citrate	224.79	48.54	91-481
Saline	308.02	68.80	125-762

Table 19

Variation of Hgb Count Between and Within Groups

Parameters	F	df	p
Between groups			
• Group	1.04	2	0.3787
• Patient (group) (between subject error)	--	15	
Within groups			
• Time	1.42	15	0.1690
• Group*time	1.38	13	0.1959
• Within subject error	--	59	

A total of 103 blood samples were analyzed for the Plt levels. The saline solution group had the highest Plt baseline level ($\bar{M} = 272.71$, $\bar{SE} = 67.96$) and mean Plt levels ($\bar{M} = 308.02$, $\bar{SE} = 68.80$), compared to the Trisodium Citrate and heparin solution groups (Table 18). This difference was not statistically significant between groups on mean platelet levels ($F [2,15; N = 103] = 0.59$, $p = 0.5651$). There was a statistically significant increase over time in mean platelet levels, but not above clinical normal values ($F [15,57; N = 103] = 4.59$, $p = 0.0001$). Table 20 presents the variation of platelets within and between groups.

Table 20

Variation of Platelets Count Between and Within Groups

Parameters	F	df	p
Between groups			
• Group	0.59	2	0.5651
• Patient (group)	--	15	
(between subject error)			
Within groups			
• Time	4.59	15	0.0001
• Group*time	0.36	13	0.9755
• Within subject error	--	57	

Serum Ionized Calcium

The final hypothesis tested was that there will be no decrease in serum ionized calcium in patients when the CVC is flushed with 4% Trisodium Citrate. A repeated measures ANOVA was used to analyze this variable for the 4% Trisodium Citrate solution group only. A total of 33 blood samples were analyzed

for serum ionized calcium (Table 21). There was no significant change in mean serum ionized calcium levels over time ($F [6,20; N = 33] = 0.35, p = 0.9041$; Table 22).

Table 21

Variation of Serum Ionized Calcium

<u>Ca⁺⁺ baseline</u>			
Group	<u>M</u>	<u>SE</u>	Range
Citrate	1.19	0.06	0.98-1.39

<u>Mean Ca⁺⁺ levels</u>			
Group	<u>M</u>	<u>SE</u>	Range
Citrate	1.19	0.05	0.91-1.36

Table 22

Variation of Serum Ionized Calcium Within the Trisodium Citrate Group

Parameters	<u>F</u>	<u>df</u>	<u>p</u>
Between groups			
• Patient (group) (between subject error)	--	6	
Within groups			
• Time	0.35	6	0.9041
• Within subject error	--	20	

CHAPTER FIVE

DISCUSSION

The objective of this study was to determine the efficacy of 4% Trisodium Citrate solution compared to 0.9% saline solution or diluted heparin 100U/ml solution in maintaining patency of central venous triple lumen catheter in critically ill patients. A prospective randomized pilot study was performed in a 24-bed mixed intensive care unit (ICU; trauma/surgical/medical). Data were collected between November 15th, 2000, and July 1st, 2002, at the Royal Alexandra Hospital ICU (Edmonton, Alberta). The final sample consisted of 18 patients (4 patients in the heparin group, 7 patients in the Trisodium Citrate group, and 7 patients in the saline group).

The findings of this study indicate that CVCs flushed with 1ml of 4% Trisodium Citrate have a survival time similar to that of CVCs flushed with 1 ml of diluted heparin 100U/ml or 1 ml of 0.9% saline solution. Moreover, the findings indicate that there was no increase in INR and PTT, no decrease in Hgb or platelets, and no decrease in serum ionized calcium in patients when the CVC was flushed with 1 ml of 4% Trisodium Citrate compared to the diluted heparin 100U/ml or 0.9% saline solution. Moreover, no adverse events related to the administration of 4% Trisodium Citrate were encountered during this pilot study.

A one-way ANOVA was performed to assess the impact of the age, BMI, APACHE II score, and number of flushes on CVC patency; and no statistical difference was found between groups. A Fisher's exact test showed no statistical difference on the categorical variables of gender, CVCs sites of insertion, CVCs

length, anticoagulant, administration of blood products, administration of antibiotics and CVCs tips infections between groups. When we take into consideration the impact of the variable CVCs "left" side of insertion on the survival time of the groups, a Wilcoxon test cannot be performed because failures on the left side of insertion were observed only on the saline group, making comparison impossible with the other groups. Looking at the impact of the variables CVCs "right" side of insertion on the survival time of the groups, a Wilcoxon test showed no statistical difference in the survival time.

No differences were found between groups on age, CVC site of insertion, CVC length, presence of anticoagulant, catheter tip infection, and reason for termination of the study. A statistical difference between the groups and the variable CVC side of insertion was found, with all CVCs of the Trisodium Citrate group inserted on the right side of the body.

In the majority of the cases, CVCs sites of insertion were subclavian vein insertion for the three groups. Even though subclavian CVCs insertions increase the risk of pneumothoraces, arterial puncture, and misplacement of catheter tip and catheter failure (Abidi et al., 2000; Lefrant et al., 2002), compared to femoral insertion, 66.67% of all catheter insertions were subclavian. The Trisodium Citrate solution group side of CVC insertion were all inserted in the right side of the body compared to the heparin and saline solution groups, where the insertions were distributed almost equally between the left and right side of the body. Craft et al. (1996) found that malfunction or block were more common with

Hickman catheters placed on the left side of the body; therefore, having CVCs inserted on the right side of the body may decrease catheter complications.

**Comparison of 4% Trisodium Citrate Solution, Heparin 100U/ml Solution,
and Saline Solution on CVC Patency**

In the study results, the majority of the observations were censored observations (77.78%), compared to uncensored observations (22.2%). Only a nonpatent CVC port was considered an uncensored observation. Four patients had nonpatent CVC ports (CVC failure), which represented the main study endpoint. Of the four CVC failures, one failure was in the citrate group, three were in the saline group, and none occurred in the heparin group.

The large proportion of censored observations had an important impact on the CVC total patency time. If we look at the CVCs total patency time means per group, the heparin group ($\bar{M}$ = 9655.0 [6.7 days]; $\bar{SE}$ = 4006.12), the saline group ($\bar{M}$ = 7206.14 [5 days]; $\bar{SE}$ = 1064.08), and the 4% Trisodium Citrate group ($\bar{M}$ = 5200.0 [3.6 days]; $\bar{SE}$ = 1064.08), the results may be underestimated because 85.71% of the Trisodium Citrate group, 57.14% of the saline group, and 100% of the heparin group were calculated using censored observations. Therefore, the median total patency time per group may also be underestimated. It is interesting that the saline solution group showed the highest median total patency time in minutes ($\bar{Mdn}$ = 8300 minutes [5.76 days]), compared to the heparin group ($\bar{Mdn}$ = 6237.50 minutes [4.3 days]) and the Trisodium Citrate solution group ($\bar{Mdn}$ = 5625 minutes 3.9 days)). However, the saline solution

group showed the highest catheter nonpatency rate (42.8%), compared to the Trisodium Citrate solution group (14.3%) and heparin solution group (0%).

The small number of CVC failures may have also an impact on the survival times. Therefore, the survival time results may be less precise compared to a survival time computed with only uncensored values. Looking closely at the results, the median survival time of 4% Trisodium Citrate solution of 5760 minutes (4 days) was estimated, with only one CVC failure. Moreover, the median survival time of the heparin solution group was not established because no CVC failure was encountered during the study. The saline solution median survival time was measured based on three CVC failures. Even though a Wilcoxon test showed no statistical difference between the three solutions in survival time, the result may be underestimated because of the small number of uncensored observations (four CVC failures) used to analyze the data.

In a recent prospective randomized study, Rabe et al. (2002) tested the effectiveness of sodium chloride 0.9%, vitamin C (200mg/ml), and heparin (5000 IU/ml) for maintaining patency of central venous triple lumen catheters. A median survival time of 10 days was found in the heparin group (5000 IU/ml), with two catheter failures (6%). In the current study, no survival time was calculated for the heparin group; only a median total patency time of 6237.50 was established. Therefore, comparison between the two studies and the two different heparin concentrations was impossible because one study took into consideration the censored data with a median survival time result and the current study cannot

take into consideration the censored result because no failure has been encountered. However, a failure rate of 6% ($N = 33$) for the heparin group (5000 IU/ml) is greater than the 0% failure rate in the current study with heparin 100 IU/ml ($N = 4$). Thus, it may be possible to achieve local anticoagulation of CVCs with lower heparin concentrations (100 IU/ml) than with high-dose heparin (5000 IU/ml).

The Trisodium Citrate solution showed a median survival time of 4 days, which is less than the median survival time of 6.5 days for the saline solution 0.9%. In comparison to the Rabe et al. (2002) study, the Trisodium Citrate solution showed a lower median survival time than did the heparin solution (10 days), the saline solution (6 days), and the vitamin C solution (6 days). The Trisodium citrate solution presented a catheter failure rate of 14.3%, which is less than the vitamin C solution ($N = 33$, 36.4%) and the saline solution ($N = 33$, 27.3% and $N = 7$, 42.8%). However, catheters filled with the Trisodium Citrate solution showed higher catheter failure rate (14.3%) than did the catheters filled with the heparin solution 5000 IU/ml ($N = 33$, 6%) and the diluted heparin solution 100 IU/ml ($N = 4$, 0%). Therefore, 4% Trisodium Citrate may be considered an alternative anticoagulant to a heparin solution (5000 IU/ml and 100 IU/ml) based on a low catheter failure rate, compared to a saline solution or a vitamin C solution.

Moreover, in the same study, Rabe et al. (2002) found that the median survival time of the saline group was 6 days ($N = 33$) with a catheter failure rate of 27.3% (9 catheters occluded/33 catheters). These results are similar to this

study's results of a median survival time of 6.5 days with a catheter failure rate of 42.8% ($N = 7$). In the Rabe et al. study, the results showed that saline solution does not prolong CVC patency compared to catheters sealed with heparin (5000 IU/ml). In the current study it was impossible to know whether 0.9% saline solution prolonged the CVC survival time compared to diluted heparin 100 IU/ml because it was not possible to compute a survival estimate for the heparin solution. However, catheters filled with 0.9% saline solution do not decrease catheter failure rate, compared to a heparin solution (100 IU/ml or 5000 IU/ml). A catheter filled with saline solution is more likely to occlude than those sealed with heparin solutions (100 IU/ml and 1000 IU/ml) or 4% Trisodium Citrate.

The findings of the current study indicate that CVCs flushed with 1ml of 4% Trisodium Citrate do not have a longer survival time than CVCs flushed with diluted heparin 100U/ml or saline solution. However, if we look only at the number of failures per group, 4% Trisodium Citrate may be clinically efficacious for maintaining CVCs patency based on one CVC failure rate (14.2%, $N = 7$).

The question of which heparin concentration should be used to prevent catheter occlusion is not clear at the moment. Rabe et al. (2002) and my study are the only randomized prospective clinical trials ever conducted that look at the use of heparin (5000 IU/ml and 100 IU/ml) for keeping central venous triple lumen catheters open. Therefore, more research is needed.

Safety of 4% Trisodium Citrate Solution

A concern about 4% Trisodium Citrate injection for maintaining patency of central venous triple lumen catheters was the unknown effect on blood

coagulation parameters (INR/PTT) and on the blood count (hemoglobin and platelets). Moreover, concerns about a decrease in serum ionized calcium related to the administration of 4% Trisodium Citrate, and the risk of complications associated with this situation (arrhythmias) were other concerns. Even though 1ml of 4% Trisodium Citrate injected into the CVC ports was safe, based on a previous study (Bunker et al., 1962), more data on the safety of 4% Trisodium Citrate for maintaining patency of CVCs for critically ill patients are needed because these results are based on a small sample ($N = 7$).

The findings indicated that 1ml of 4% Trisodium Citrate injected either to 16cm- or 20cm-length CVCs did not increase INR or PTT for these critically ill patients. Moreover, no decrease in hemoglobin, platelets, and serum ionized calcium were detected. Also, no adverse events were recorded during the study. Therefore, based on a sample size of seven patients who received the Citrate solution, the results show that 1ml of 4% Trisodium Citrate may be safely used without any adverse events for maintaining the patency of 16cm- or 20cm-length central venous triple lumen catheter in critically ill patients.

Implications of the Study

This study was the first one done that considered the use of 4% Trisodium Citrate for maintaining the patency of CVCs. Although interesting data were obtained, altering practice based on these findings is not warranted. However, the use of saline solution for maintaining the patency of triple lumen catheters for critically ill patients raises a concern based on a CVC failure rate of 42.8% ($N = 7$). The use of 4% Trisodium Citrate solution may be considered and preferred to

saline solution as an alternative to diluted heparin for maintaining the patency of CVCs for critically ill patients because of a low failure rate and its safety for critically ill patients. Moreover, the use of 1ml of 4% Trisodium Citrate solution to flush 16cm or 20cm central venous triple lumen catheters did not alter blood coagulation parameters (INR/PTT), blood count (hemoglobin, platelets), or serum ionized calcium and can be safely used for critically ill patients. The question of whether a more dilute heparin solution such as 100 IU/ml compared to 5000 IU/ml can be used to prevent catheter occlusion is not clear.

Limitations of the Study

Most of the patients were admitted for respiratory diseases, GI problems, sepsis, and trauma. Therefore the results of this study may not be directly applicable to patients with neurological and metabolic diseases because there were only a limited number of such patients included in the study.

Adherence to protocol and consistency between nurses presented a challenge. Moreover, staff turnover and nursing work load were factors that may have influenced the sample size of this study.

Because this was a pilot study with a small sample size ($n=18$) and the majority of the data on the survival analysis were censored observations, the results on CVCs patency rate and survival estimates must be interpreted with caution. More research is needed to clearly establish the efficacy of 4% Trisodium Citrate as an anticoagulant for maintaining the patency of central venous triple lumen catheters.

An important limitation of the study is related to the catheter tip position. Recent studies identified catheter tip position as an important risk factor for catheter occlusion or catheter-related thrombosis in venous ports (Caers, Fontaine, Ponnet, Velkeniers, & Lacor, 2001; Luciani et al., 2001; Petersen, Delaney, Brakstad, Rowbotham, & Bagley, 1999) and in peripherally inserted central lines in children (Racadio, Doellman, Johnson, Bean, & Jacobs, 2001). Even though all catheters inserted in the internal jugular and subclavian vein had a chest x-ray to confirm catheter placement, no systematic procedure was established in the current study for confirming placement. Catheter tip position may have an impact on the catheter failure rate.

Conclusion

Improving patient care and decreasing complications for critically ill patients are the objectives of doing nursing research. Despite the limitations of this clinical trial, the findings provide a valuable comparison of diluted heparin, 4% Trisodium Citrate, and saline solution for maintaining the patency of CVCs for critically ill patients.

A median survival time of 6.5 days for the 0.9% saline group and 4 days for the Trisodium Citrate group have been calculated. Even though the saline solution showed the highest median survival time, it also showed the highest catheter nonpatency rate (42.8%) compared to the Trisodium Citrate solution group (14.3%) and the heparin solution group (0%). A catheter filled with saline solution is more likely to occlude than are those sealed with heparin solutions (100 IU/ml) or 4% Trisodium Citrate. Therefore, 4% Trisodium Citrate shows

promise as an alternative anticoagulant to diluted heparin solution 100 IU/ml based on a low catheter failure rate compared to a saline solution.

The findings of this study indicate that CVCs flushed with 1ml of 4% Trisodium Citrate have a similar survival time to that of CVCs flushed with 1 ml of diluted heparin 100U/ml or 1 ml of 0.9% saline solution. Moreover, the findings indicate that there was no increase in INR and PTT, no decrease in Hgb or platelets, and no decrease in serum ionized calcium in patients when the CVC was flushed with 1 ml of 4% Trisodium Citrate, compared to diluted heparin 100U/ml or 0.9% saline solution. Moreover, no adverse events related to the administration of 4% Trisodium Citrate were encountered during this study. However, the findings provide further support for continuing investigations to discover the optimal regimen to maintain patent CVC ports.

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APPENDIX A

TRISODIUM CITRATE RESEARCH STUDY

ENROLLMENT ASSESSMENT

Initials F,M,L _____ Hosp # _____ AB# _____ Study # _____
 DOB _____ Age _____ Ht (cm) _____ Wt (kg) _____
 Hosp admit _____ Phone# _____ Sex _____ Race _____
 ICU admit d/t _____ ICU admit
 dx _____

INCLUSION

___ Age 18

___ Patient admitted to the intensive care unit.

___ Has a central venous triple lumen access (subclavian, jugular, or femoral) inserted for medical reasons.

___ Not receiving any medications known to affect coagulation (investigational agent, coumadin, intravenous heparin, streptokinase, urokinase, t-PA) for at least 3 days prior to the beginning of the study. Only patient with subcutaneous prophylactic heparin, ASA, and low molecular weight heparin may be enrolled.

EXCLUSION

Contraindications to the use of heparin:

- ___ History of heparin induced thrombocytopenia;
- ___ Previous untoward reaction to heparin;
- ___ Thrombocytopenia (platelet count < 40,000/mm³);
- ___ Evidence of non-reversible coagulopathy (INR >2.5 or PTT >70 or fibrinogen <1.00gm/l);
- ___ Clinical judgement of physician when active bleeding from surgical/traumatic wounds or cerebral hemorrhage happen.

Contraindications to the use of 4% Trisodium Citrate anticoagulation:

- ___ Profound metabolic or respiratory alkalosis (serum pH>7.60);
- ___ Serum sodium >160 mmol/l.

___ Insertion of the CVC which took place outside the ICU.

Consent obtained d/t: _____

Randomize as per Pharmacy Department. (RAH 477-4460) d/t _____

Get study solution from Pharmacy and CVC line from office d/t _____

Within 24 hr pre catheter insertion:

APACHE II _____ INR _____ PTT _____ Hb _____ PLT _____

Orders:

Enroll in Trisodium Citrate Research Study - Group A or B or C
Flush 1 ml. of study solution q24h to unused central line ports with 10 ml syringe
Daily lab work per unit protocol
Ionized calcium within 2 h post-catheter insertion and then daily,
When catheter removed, send tip for C/S
Clean central line daily with 0.5% Chlorhexidine in 70% isopropyl alcohol

Chart: <pt name> has been assessed for the trisodium citrate study and fulfills entry criteria.
The study was discussed with _____. Purpose, procedures, risks and benefits of the study were explained by _____ as well as issues of confidentiality and voluntary participation (as outlined in the information sheet). Questions and concerns were answered/discussed. Consent for participation was obtained from _____ at _____ h. No study procedures were done prior to obtaining consent.

Baxter Catheter: size _____ inserted d/t _____ site _____

IF THE PATIENT IS TRANSFERRED**ORDERS:**

Trisodium Citrate Research Study - Group ____ (A or B or C)
Flush 1 ml. of study solution q24h to unused central line ports with 10 ml syringe
CBC daily
PT/PTT daily
Ionized Calcium daily (green top tube send to ICU lab for analysis)
Clean central line daily with 0.5% Chlorhexidine in 70% isopropyl alcohol

Explain procedure to the admitting nurse: _____

APPENDIX B**TRISODIUM CITRATE RESEARCH STUDY****RESEARCH ASSISTANT GUIDE**

Once patient meets study inclusion criteria and study consent is obtained:

1. Collects data collection package.
2. Checks to make sure patient doesn't meet any exclusion criteria.
3. Call Pharmacy Department at extension 4464 for randomization group and study numbers (as close time as possible of starting study).
4. Get supply of study solution, from pharmacy and leave solution at bedside.
5. Bring the central venous triple lumen catheter at the bedside to be inserted.
6. Write study orders on the physician order sheet.
7. Give instructions to the nursing staff.
8. Leave in front of the chart: nursing instructions, bedside worksheet, and summary of the study.
9. Post the study bedside sheet in the room.
10. Make sure a INR/PTT (one blue top), ionized calcium (from arterial blood gas) and complete blood count (one mauve top) is drawn. Record date and time, and attach appropriate patient labels to it.
11. Record APACHE II score.
12. Record initial data on Data Collection worksheet and case report.
13. Add to Kardex to page Research Assistant if any concerns or problems.
14. Record in Enrollment Log, in the research binder.

PATIENT TRANSFERRED:

15. Write study transfer orders on the physician order sheet.
16. Make sure the vials are transferred with the patient.
17. Give instructions to the nursing staff.
18. Leave in front of the chart: nursing instructions, bedside worksheet, and summary of the study.
19. Post the study bedside sheet in the room.
20. Add to Kardex to page Research Assistant if any concerns or problems.

APPENDIX C

TRISODIUM CITRATE RESEARCH STUDY

INFORMATION LETTER (FAMILY)

Title of project: Efficacy of 4% Trisodium Citrate Compared to Saline or Diluted Heparin Solution in Patency of Central Venous Triple Lumen Catheters in Critically Ill Patients

Principal Investigators:

Dominique Michaud, RN, MN Candidate
Phone: 780-491-5696

Louise Jensen, RN, PhD
Phone: 780-492-6795

Co-Investigators:

T. Larson, RN; S. Currie, RN; T. Tanguay, RN; E. Konopad, MN; K. Forgach, BScPharm;
D. J. Kutsogiannis, MD; D. Stollery, MD

Purpose of the Study: When you are sick in intensive care, a soft plastic tube is inserted into your vein to give some drugs and/or fluids. This tube is called a central venous catheter. To keep the tube from plugging, a drug is put into the tubing. This is called "flushing". The drug most often used is a blood thinner called heparin. The reason we are doing the study is to see if a drug called 4% Trisodium Citrate is better than salt water or diluted heparin in stopping the tube from plugging in sick patients.

Study Procedures: Having a central venous catheter inserted is part of the routine care of a patient in the intensive care. If your relative takes part in the study, he/she will be assigned to one of the three solutions (4% Trisodium Citrate, salt water, or diluted heparin). Your relative will have the catheter tubing flushed with the assigned drugs. You or the study investigators will not know which drug is used.

Risks: There is no additional risks or discomfort associated with your relative taking part in this study. It is possible that one of the three solutions is less effective than the others. It may lead to more plugging of the tubing. You will be told if any problems occur with the catheter plugging.

Benefits: There is no way to be certain that your relative will benefit from taking part in this study. The results of this study may improve nursing care.

Voluntary Participation: Agreeing to have your relative take part in this study is up to you. If you do not want your relative to be in the study, your relative's care will not change. If you change your mind after you have agreed to have your relative take part in the study, you can stop the study at any time without changing his/her care. Your relative will be told of his/her enrollment (if possible) and given the opportunity to withdraw.

Trisodium Citrate Research Study

Information Sheet (Patient)

Title of project: Efficacy of 4% Trisodium Citrate Compared to Saline or Diluted Heparin Solution in Patency of Central Venous Triple Lumen Catheters in Critically Ill Patients

Compensation: There will be no monetary costs to you for taking part in this study. You will not be charged for the drug(s) or any procedures. By signing this consent form, you are not releasing the investigator(s), institution(s) and/or sponsor(s) from their legal and professional responsibilities.

Confidentiality: The information collected for this study will be kept private. People employed by the Trisodium Citrate Research Study may look at your hospital chart. Your name will not be used. If you have any questions about the study at any time, please do not hesitate to call the Critical Care Research Office (Royal Alexandra Hospital) at 477-4096 and ask to speak to one of the investigators. If you have concerns about any aspect of this study, you may contact the Capital Health Authority patient representative at 407-1040. This office has no affiliation to the study or the investigators.

Consent Form (Family)

Title of project: Efficacy of 4% Trisodium Citrate Compared to Saline or Diluted Heparin Solution
in Patency of Central Venous Triple Lumen Catheters in
Critically Ill Patients

Principal Investigators:

Dominique Michaud, RN, MN Candidate
Phone: 780-491-5696

Louise Jensen, RN, PhD
Phone: 780-492-6795

Yes No

Do you understand that you have been asked to have your relative take part in a research study?

Have you read and received a copy of the attached Information Sheet?

Do you understand the risks and benefits involved in your relative's taking part in this research study?

Have you had a chance to ask questions and discuss this study?

Do you understand that you are free to withdraw your relative from the study at any time, without having to give a reason and without affecting your relative's care?

Has the issue of confidentiality been explained to you, and do you understand who will have access to your relative's medical records?

Would you like us to tell your relative's family doctor () about your relative taking part in this study?

Who explained the study to you? _____

I agree to have my relative _____ take part in this study.

Signature of _____
Relative: _____ **Date/time** _____
Printed name /Relationship: _____

Signature of Witness: _____ **Date/time** _____
Printed name: _____

I believe that the person signing this form understands what is involved in the study and voluntarily agrees to participate.

Signature of Investigator or Designee: _____ **Date** _____

APPENDIX D
TRISODIUM CITRATE RESEARCH STUDY
INFORMATION SHEET (PATIENT)

Title of project: Efficacy of 4% Trisodium Citrate Compared to Saline or Diluted Heparin Solution in Patency of Central Venous Triple Lumen Catheters in Critically Ill Patients

Principal Investigators:

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T. Larson, RN; S. Currie, RN; T. Tanguay, RN; E. Konopad, MN; K. Forgach, BScPharm;
D. J. Kutsogiannis, MD; D. Stollery, MD

Purpose of the Study: When you are sick in intensive care, a soft plastic tube is inserted into your vein to give some drugs and/or fluids. This tube is called a central venous catheter. To keep the tube from plugging, a drug is put into the tubing. This is called "flushing". The drug most often used is a blood thinner called heparin. The reason we are doing the study is to see if a drug called 4% Trisodium Citrate is better than salt water or diluted heparin in stopping the tube from plugging in sick patients.

Study Procedures: Having a central venous catheter inserted is part of the routine care of a patient in the intensive care. If you take part in the study, you will be assigned to one of the three solutions (4% Trisodium Citrate, salt water, or diluted heparin). You will have the catheter tubing flushed with the assigned drugs. You or the study investigators will not know which drug is used.

Risks: There is no additional risks or discomfort associated with you taking part in this study. It is possible that one of the three solutions is less effective than the others. It may lead to more plugging of the tubing. You will be told if any problems occur with the catheter plugging.

Benefits: There is no way to be certain that you will benefit from taking part in this study. The results of this study may improve nursing care.

Voluntary Participation: Agreeing to be involved in this study is up to you. If you do not want to be in the study, your care will not change. If you change your mind after you have agreed to take part in the study, you can stop the study at any time without affecting your care.

Trisodium Citrate Research Study**Information Sheet (Patient)**

Title of project: Efficacy of 4% Trisodium Citrate Compared to Saline or Diluted Heparin Solution in Patency of Central Venous Triple Lumen Catheters in Critically Ill Patients

Compensation: There will be no monetary costs to you for taking part in this study. You will not be charged for the drug(s) or any procedures. By signing this consent form, you are not releasing the investigator(s), institution(s) and/or sponsor(s) from their legal and professional responsibilities.

Confidentiality: The information collected for this study will be kept private. People employed by the Trisodium Citrate Research Study may look at your hospital chart. Your name will not be used. If you have any questions about the study at any time, please do not hesitate to call the Critical Care Research Office (Royal Alexandra Hospital) at 477-4096 and ask to speak to one of the investigators. If you have concerns about any aspect of this study, you may contact the Capital Health Authority patient representative at 407-1040. This office has no affiliation to the study or the investigators.

Consent Form (Patient)

Title of project: Efficacy of 4% Trisodium Citrate Compared to Saline or Diluted Heparin Solution in Patency of Central Venous Triple Lumen Catheters in Critically Ill Patients

Principal Investigators:

Dominique Michaud, RN, MN Candidate
Phone: 780-491-5696

Louise Jensen, RN, PhD
Phone: 780-492-6795

Yes No

Do you understand that you have been asked to be in a research study?

Have you read and received a copy of the attached information sheet?

Do you understand the risks and benefits involved in taking part in this research study?

Have you had an opportunity to ask questions and discuss this study?

Do you understand that you are free to withdraw your from the study at any time, without having to give a reason and without affecting your care?

Has the issue of confidentiality been explained to you? Do you understand who will have access to your records?

Do you want the investigators to inform your family doctor that you are participating in this research study? If so, please provide your doctor's name:

This study was explained to me by: _____

I agree to take part in this study:

Signature of Research Participant

Date

Witness

Printed Name

Printed Name

I believe that the person signing this form understands what is involved in the study and voluntarily agrees to participate.

Signature of Investigator or Designee

Date

APPENDIX E

TRISODIUM CITRATE RESEARCH STUDY

RANDOM ASSIGNMENT SHEET

Date	Initials	Group/solution	Study #	Study site name
		B	TC 001	
		A		
		C		
		B		
		B		
		B		
		C		
		A		
		A		
		C		
		A		
		C		
		C		
		B		
		B		
		B		
		B		
		C		
		C		
		A		
		C		
		A		
		A		
		A		
		A		
		B		
		C		
		A		
		C		
		B		
		B		
		C		
		C		
		B		
		A		
		A		
		A		

Random Assignment Sheet

Date	Initials	Group/solution	Study #	Study site name
		C		
		B		
		B		
		B		
		B		
		C		
		C		
		A		
		C		
		A		
		A		
		A		
		B		
		C		
		A		
		C		
		C		
		C		
		A		
		A		
		B		
		A		
		B		
		B		
		C		
		C		
		C		
		C		
		A		
		A		
		B		
		B		
		B		
		A		
		A		
		B		

Random Assignment Sheet

Date	Initials	Group/solution	Study #	Study site name
		B		
		A		
		C		
		A		
		A		
		B		
		C		
		A		
		C		
		B		
		B		
		C		
		A		
		B		
		A		
		B		
		B		
		C		
		A		
		C		
		B		
		C		
		C		
		A		
		C		
		B		
		B		
		C		
		B		
		A		
		C		
		A		
		A		
		B		
		C		
		A		

Random Assignment Sheet

Date	Initials	Group/solution	Study #	Study site name
		C		
		B		
		A		
		B		
		C		
		C		
		B		
		A		
		A		
		B		
		C		
		A		

APPENDIX F
TRISODIUM CITRATE RESEARCH STUDY
PHARMACY PROCEDURE

1. It will be the responsibility of the Pharmacy Department at the Royal Alexandra Hospital to prepare.
2. Pharmacy will be notified by the research assistant when a patient meets the inclusion criteria. The Pharmacy Department will then assign a group and study number to the patient and will follow the Random Assignment Sheet for patient assignment.
3. The Pharmacy Departments will dispense the study solutions.
4. The Random Assignment Sheet will be completed as indicated for date, initials, group/solution, study number, and study site name.
5. The research assistant should then record the patient's randomization group and study number on all appropriate documents.
6. For night enrolment, the Pharmacist on-call will be paged for randomization and dispense of study solution.

APPENDIX G
TRISODIUM CITRATE RESEARCH STUDY
STAFF NURSE INSTRUCTIONS

This study involves administering either 4% Trisodium Citrate, saline, or diluted heparin solution for flushing central venous triple lumen catheters. The directions for administration as well as your role in the study are outlined below. For a summary of the study, please refer to the summary sheet in this patient's chart or ask the research assistant.

Nurse's Role

1. Only a Baxter central venous triple lumen catheter (stock # M316 F or #M320 F) can be inserted for the study.
2. Any site (femoral/jugular/subclavian) can be used for the study.
3. Only 0.5% chlorhexidine gluconate and 70% isopropyl alcohol solution will be used to clean the catheter insertion site.
4. A sterile 4x4 gauze folded in half will be used to cover the catheter exit site and attached with mefix tape. The four sides of the gauze must be covered.
5. Document date and time of catheter insertion and site and type of catheter
6. Flush each port that will be locked with 10cc of injectable normal saline **PRIOR** to the administration of the study solution.
7. 4% Trisodium Citrate/saline/diluted heparin (study solution) will be administered through the port of then central venous catheter.
8. If medications are given intermittently or blood samples drawn from the port, flush each port with 10cc of injectable normal saline prior to the administration of the study solution.
9. Only 1ml of study solution will be used to flush each port.
10. If more study solution is needed, the Pharmacy Department will be called at Ext. 4460, or the unit manager will be informed.
11. Only a 10 ml syringe will be used to flush the ports.
12. Any of the ports can be flushed with the study solution.
13. A positive pressure technique will always be used to flush any of the ports.
14. The times of the administration of the study solution and which port has been flushed will be documented in the bedside worksheet.
15. Any solution, blood product, or medication being infused in EACH PORT will be indicated in the bedside worksheet.
16. **The time and rate** of antibiotics, anticoagulant, continuous infusion/maintenance IV and blood product will be documented in the bedside worksheet
17. The date and time when a central venous catheter is removed and the reason will be documented in the bedside worksheet.
18. If a port is non-patent the date, time and which port must be documented
19. The study solution of another patient **WILL NOT BE USED**
20. The study stops when a port is non-patent, the CVC is removed/changed/rewired, patient meets the exclusion criteria or is withdrawn from the study.

Staff Nurse Instructions

21. If you transfer the patient with the CVC, the **STUDY WILL CONTINUE**. Call the Research Nurse to let her know.

**IF YOU HAVE ANY QUESTIONS OR CONCERNS
PLEASE CALL THE RESEARCH NURSE ON CALL**

APPENDIX H

TRISODIUM CITRATE RESEARCH STUDY

SUMMARY OF THE STUDY

Title of project: Efficacy of 4% Trisodium Citrate Compared to Saline or Diluted Heparin Solution in Patency of Central Venous Triple Lumen Catheters in Critically Ill Patients

Principal Investigators:

Dominique Michaud, RN, MN Candidate
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Phone: 780-492-6795

Co-Investigators:

T. Larson, RN; S. Currie, RN; T. Tanguay, RN; E. Konopad, MN; K. Forgach, BScPharm;
D. J. Kutsogiannis, MD; D. Stollery, MD

Summary: In the Intensive Care Unit (ICU), central venous catheters are frequently used as a temporary vascular access for critically ill patients. Catheter-related occlusion is the most common noninfectious complication seen with central venous access in the ICU setting. The debate continues as to which solution to use, diluted heparin or saline, in preventing central venous catheter lumen thrombosis. Moreover, bleeding and heparin-induced thrombocytopenia have been associated with diluted heparin when used as a flushing solution. An alternative to diluted heparin or saline solution for flushing central venous catheters is 4% Trisodium Citrate solution. The objective of this study to determine the efficacy of 4% Trisodium Citrate solution compared to saline or diluted heparin 100 U/ml solution in maintaining central venous triple lumen catheter patency in critically ill patients.

The study will be a double-blind, randomized, controlled trial. All patients admitted to the ICU at the Royal Alexandra Hospital will be evaluated for admission into this feasibility study. Using a block random assignment procedure, a total of 120 patients meeting the inclusion criteria will be enrolled. We are expecting a 20% enrollment, which is 24 patients per month. Considering all these factors, the time period for the data collection will be approximately five months. The patients will be randomized to one of three study solution groups, A, B, or C (4% Trisodium Citrate, saline or diluted heparin solution) by the Pharmacy Department. The Critical Care Research Team will be in charge of the data collection on a daily basis.

APPENDIX I

TRISODIUM CITRATE RESEARCH STUDY

BEDSIDE SHEET

THIS PATIENT IS IN
THE
TRISODIUM CITRATE
STUDY

IF YOU HAVE ANY
QUESTIONS OR
CONCERNS, PLEASE
CONTACT
RESEARCH RN

APPENDIX J

TRISODIUM CITRATE RESEARCH STUDY

ENROLMENT LOG ON UNIT

[illegible]

APPENDIX K
TRISODIUM CITRATE RESEARCH STUDY
EXCLUSION LOG

[illegible]

APPENDIX L

TRISODIUM CITRATE RESEARCH STUDY

ADVERSE EVENTS

Adverse Events To be completed for all adverse events that occur from initiation of the citrate study to 3 days after the completion of the study. For bleeding events, record from the initiation of the study to 3 days after the completion of the study.

1. Initials: ____ 2. Study number: ____ 3. Group: ____

Event	Start Date (day/month/yr)	Stop Date (day/month/yr)	Treatment Yes(1) No(2)	If Bleed: Code therapy (as below)

Therapy for bleed codes (enter all that apply): (0) No therapy
 (1) Transfusions only
 (2) Local therapy: i.e., endoscopic
 injection, pressure/packing at site for >
 30 minutes
 (3) Surgery to control bleeding

APPENDIX M
TRISODIUM CITRATE RESEARCH STUDY
APACHE II SCORE

Initials _____ Study # _____ Group # _____ Hospital # _____

_____ GCS (15 minus worst GCS(____)=# points)

AaDO₂: = (FiO₂ x 653) - PaCO₂-PaO₂ Start d/t _____ End d/t _____

Variable	4	3	2	1	0	1	2	3	4
Temp	≥41	39-40.9		38.5-38.9	36-38.4	34-35.9	32-33.9	30-31.9	≤29.9
HR	≥180	140-179	110-139		70-109		55-69	40-54	≤39
RR	≥50	35-49		25-34	12-24	10-11	6-9		≤5
MAP	≥160	130-159	110-129		70-109		50-69		≤49

If FiO₂ ≥ 0.5, use ABG with highest AaDO₂; If FiO₂ < 0.5, use ABG with lowest PaO₂

PaO ₂					>70	61-70		55-60	<55
AaDO ₂	≥500	350-499	200-349		< 200				
pH	≥7.7	7.6-7.69		7.5-7.59	7.33-7.49		7.25-7.32	7.15-7.24	<7.15
HCT	≥60		50-59.9	46-49.9	30-45.9		20-29.9		< 20
WBC	≥40		20-39.9	15-19.9	3-14.9		1-2.9		< 1
NA	≥180	160-179	155-159	150-154	130-149		120-129	111-119	≤ 110
K	≥7	6-6.9		5.5-5.9	3.5-5.4	3-3.4	2.5-2.9		< 2.5
HCO ₃	≥52	41-51.9		32-40.9	22-31.9		18-21.9	15-17.9	< 15
* Cr	≥309	177-309	133-176		53-132		53		

*only do HCO₃ if no ABG * Double APACHE points for Cr if in acute renal failure

_____ Total APS Points

Age Points:

0 ≤ 44

_____ Age Points

2 45-54

_____ Chronic Health Points

3 55-64

_____ Total APACHE (≥ 10 to enroll)

5 65-74

Chronic Health Conditions None

6 ≥ 75

_____ Elective OR (1 point)

_____ Nonoperative or emerg OR (5 points)

APACHE II Score

- **Liver:** Biopsy proven cirrhosis & documented portal hypertension or past upper GI bld due to portal hypertension or prior hepatic failure/encephalopathy/coma
- **Cardiovascular:** Angina or SOB at rest or minimal exertion i.e., self-care (NYHA IV)
- **Respiratory:** Chronic restrictive, obstructive, or vascular disease resulting in severe exercise restriction (unable to climb stairs, perform household duties) or documented chronic hypoxia, hypercapnia, secondary polycythemia, severe pulmonary hypertension (>40 mmHg) or respirator dependency
- **Renal:** Receiving chronic hemo/peritoneal dialysis
- **Immunosuppressed:** Received therapy that suppresses resistance to infection, i.e., chemotherapy, radiation, long-term low dose steroids (during 30 days prior to hospitalization), or recent high dose steroids (>15 mg/kg for >5 days) or disease that is sufficiently advanced to suppress resistance to infection, i.e., leukemia, lymphoma, AIDS, metastatic CA.

APPENDIX N

TRISODIUM CITRATE RESEARCH STUDY

CASE REPORT FORM

Initials: _____

Study # : _____

Group: _____

1. Date of birth: DD MMM YYYY Age: years
2. Sex: ☐ Male ☐ Female
3. Date and time of admission to hospital: DD MMM YYYY
4. 1ST ICU admission Dx: ☐ (See Appendix O: Admission Toxonomy)
5. APACHE II Score: ☐ (See Appendix M: APACHE II score)
6. Date and time of admission to ICU: DD MMM YYYY
7. Body mass index : Weight: Kg Height cm

CATHETERS

8. Date and time of catheter insertion: DD MMM YYYY Time
9. Site of catheter insertion: IJ ☐ Femora ☐ Subclavian ☐
10. Side of insertion: Left ☐ Right ☐
11. Length of catheter: cm
12. Date and time of nonpatent port: DD MMM YYYY
13. Other reason for termination of the study: _____

Case Report Form

14- LABORATORY

Day 1 = Time line insertion until 0700

Days	INR	PTT	HGB	PLT	Ionized calcium
Baseline					
Day 1					
Day 2					
Day 3					
Day 4					
Day 5					
Day 6					
Day 7					
Day 8					
Day 9					
Day 10					
Day 11					
Day 12					
Day 13					
Day 14					
Day 15					

15. Date/time that catheter became nonpatent, changed, rewired or removed:

16. Administration of anticoagulant

Date/type: _____

Date/type: _____

Date/type: _____

17. Locked (minutes):

Proximal: _____

Medial: _____

Distal: _____

18. Number of flushes:

Proximal: _____

Medial: _____ Distal: _____

Case Report Form

19. Variables

Day	Port	Pump (P)	Gravity (G)	Mixed P/G	Infusion rate Low/high/mean	Locked (min)	# Flushes
Day 1	Prox						
	Med						
	Dist						
Day 2	Prox						
	Med						
	Dist						
Day 3	Prox						
	Med						
	Dist						
Day 4	Prox						
	Med						
	Dist						
Day 5	Prox						
	Med						
	Dist						
Day 6	Prox						
	Med						
	Dist						
Day 7	Prox						
	Med						
	Dist						
Day 8	Prox						
	Med						
	Dist						
Day 9	Prox						
	Med						
	Dist						
Day 10	Prox						
	Med						
	Dist						
Day 11	Prox						
	Med						
	Dist						
Day 12	Prox						
	Med						
	Dist						
Day 13	Prox						
	Med						
	Dist						
Day 14	Prox						
	Med						
	Dist						
Day 15	Prox						
	Med						

20. Infection of the catheter tip:YES ☐ Which organism(s)? _____NO ☐**21. Protocol followed:**

Procedure for catheter insertion and choice of catheter:

YES ☐ NO ☐

Procedure for catheter site care:

YES ☐ NO ☐

Procedure for catheter flushing:

YES ☐ NO ☐**22. Exclusion from study**YES ☐ Why? _____NO ☐

Completed by: _____

APPENDIX O
TRISODIUM CITRATE RESEARCH STUDY
ADMISSION TAXONOMY

Non-operative**Cardiovascular/Vascular**

- 01 Cardiogenic Shock
- 02 Cardiac arrest
- 03 Aortic aneurysm
- 04 Congestive Heart Failure
- 05 Peripheral Vascular Disease
- 06 Rhythm disturbance
- 07 Acute myocardial infarction
- 08 Hypertension
- 09 Other cardiovascular disease

Respiratory

- 10 Parasitic pneumonia
- 11 Aspiration pneumonia
- 12 Respiratory neoplasm
- 13 Respiratory arrest
- 14 Pulmonary edema
- 15 Bacterial/viral pneumonia
- 16 Chronic obstructive pulmonary disease
- 17 Pulmonary embolism
- 18 Mechanical airway obstruction
- 19 Asthma
- 20 Other respiratory disease

Gastrointestinal

- 21 Hepatic failure
- 22 GI perforation/rupture/obstruction
- 23 GI bleeding due to varices
- 24 GI inflammatory disease ulcerative colitis, Cohn's, pancreatitis
- 25 GI vascular insufficiency
- 26 Diverticulitis or corrosive injury
- 27 GI bleed due to ulcer/laceration
- 28 GI bleed due to diverticulosis/angiodysplasia
- 29 Other GI diseases

Neurologic

- 30 Intracerebral hemorrhage/hematoma
- 31 Subarachnoid hemorrhage/intracranial aneurysm
- 32 Stroke/CVA
- 33 Neurologic infection: abscess, meningitis, inflammation
- 34 Neuromuscular disease: myasthenia gravis, Guillaine Barré
- 35 Seizure
- 36 Other neurologic diseases

Post-operative**Cardiovascular/Vascular**

- 50 Dissecting/ruptured aneurysm
- 51 Peripheral vascular disease (no bypass graft)
- 52 Valvular heart surgery
- 53 Elective abdominal aneurysm repair
- 54 Peripheral artery bypass graft
- 55 Carotid endarterectomy
- 56 Gangrenous extremity/cellulitis
- 57 Other cardiovascular diseases (CABG)

Respiratory

- 58 Respiratory infection
- 59 Lung neoplasm
- 60 Respiratory neoplasm mouth, sinus, larynx, trachea
- 61 Broncho-pleural or T-E fistula
- 62 Other respiratory diseases

Gastrointestinal

- 63 GI perforation
- 64 GI inflammatory disease
- 65 GI obstruction
- 66 GI bleeding
- 67 Liver transplant
- 68 GI neoplasm (not perforation, rupture, obstruction)
- 69 GI cholecystitis/cholangitis
- 70 Other GI diseases

Neurologic

- 71 Intracerebral hemorrhage/hematoma
- 72 Subdural/epidural hematoma

- 73 Subarachnoid hemorrhage/intracranial aneurysm

- 74 Laminectomy/other spinal cord surgery

- 75 Craniotomy for neoplasm

- 76 Other neurologic diseases

Trauma

- 77 Head trauma (with or without multiple trauma)

- 78 Multiple trauma (excl head) (incl single site)

Renal

- 79 Renal neoplasm
- 80 Other renal diseases

Gynecologic

- 81 Hysterectomy

Sepsis

- 37 Sepsis (other than urinary tract)
- 38 Sepsis of urinary tract origin

Trauma

- 39 Head trauma (with/without multiple trauma)
- 40 Multiple trauma (excl head) (incl single site)

Metabolic

- 41 Metabolic coma
- 42 Diabetic ketoacidosis
- 43 Drug overdose
- 44 Other metabolic disorders

Hematologic

- 45 Coagulopathy/neutropenia/
thrombocytopenia-DIC
- 46 Other hematologic diseases

Renal diseases:

- 47 Obstruction, bleeding, abscess

Orthopedic

- 82 Hip or extremity fracture
- 83 Patients who are only in ICU due to age